This is a digital copy of a book that was preserved for generations on library shelves before it was carefully scanned by Google as part of a project to make the world's books discoverable online.

It has survived long enough for the copyright to expire and the book to enter the public domain. A public domain book is one that was never subject to copyright or whose legal copyright term has expired. Whether a book is in the public domain may vary country to country. Public domain books are our gateways to the past, representing a wealth of history, culture and knowledge that's often difficult to discover.

Marks, notations and other marginalia present in the original volume will appear in this file - a reminder of this book's long journey from the publisher to a library and finally to you.

Usage guidelines

Google is proud to partner with libraries to digitize public domain materials and make them widely accessible. Public domain books belong to the public and we are merely their custodians. Nevertheless, this work is expensive, so in order to keep providing this resource, we have taken steps to prevent abuse by commercial parties, including placing technical restrictions on automated querying.

We also ask that you:

+ *Make non-commercial use of the files* We designed Google Book Search for use by individuals, and we request that you use these files for personal, non-commercial purposes.

+ *Refrain from automated querying* Do not send automated queries of any sort to Google's system: If you are conducting research on machine translation, optical character recognition or other areas where access to a large amount of text is helpful, please contact us. We encourage the use of public domain materials for these purposes and may be able to help.

+ *Maintain attribution* The Google "watermark" you see on each file is essential for informing people about this project and helping them find additional materials through Google Book Search. Please do not remove it.

+ *Keep it legal* Whatever your use, remember that you are responsible for ensuring that what you are doing is legal. Do not assume that just because we believe a book is in the public domain for users in the United States, that the work is also in the public domain for users in other countries. Whether a book is still in copyright varies from country to country, and we can't offer guidance on whether any specific use of any specific book is allowed. Please do not assume that a book's appearance in Google Book Search means it can be used in any manner anywhere in the world. Copyright infringement liability can be quite severe.

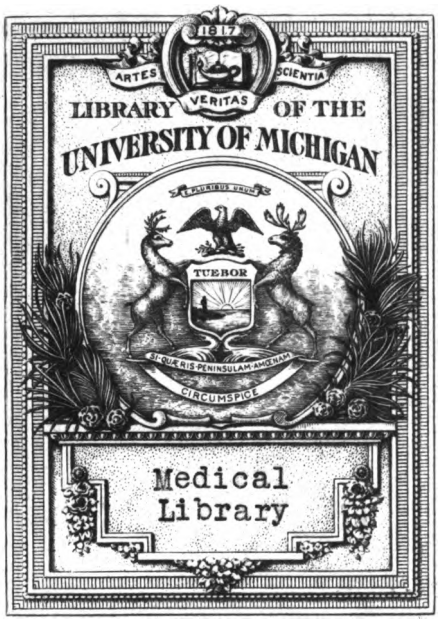
About Google Book Search

Google's mission is to organize the world's information and to make it universally accessible and useful. Google Book Search helps readers discover the world's books while helping authors and publishers reach new audiences. You can search through the full text of this book on the web at `http://books.google.com/`

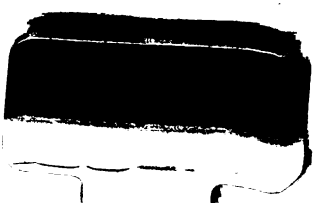
B 3 9015 00221 943 7
University of Michigan – BUHR

Digitized by Google

LIBRARY OF
GEO. SLOCUM.
NO.



Bequest of
Dr.George Slocum



Digitized by Google

610.5
A5
M5
A8

Digitized by Google

Digitized by Google

Digitized by Google

Digitized by Google

TRANSACTIONS OF THE

SECTION ON

Pathology and Physiology

of the
American Medical Association
at the Seventy-Third Annual
Session, held at St. Louis, Mo.,
May 22 to 26, 1922

AMERICAN MEDICAL ASSOCIATION PRESS
CHICAGO: NINETEEN HUNDRED AND TWENTY-TWO

Digitized by Google

Reprinted from
THE JOURNAL
of the
AMERICAN MEDICAL ASSOCIATION

Copyright, 1922
by the
American Medical Association

Digitized by Google

Med. Lib.
Bequest of
Dr. D. Bengt Steenum
5-23-1933

OFFICERS FOR 1921-1922

CHAIRMAN

JOHN A. KOLMER - - - - - - PHILADELPHIA

SECRETARY

J. J. MOORE - - - - - - - - - CHICAGO

EXECUTIVE COMMITTEE

FRANCIS CARTER WOOD, NEW YORK
HOWARD T. KARSNER, CLEVELAND
E. R. LECOUNT, CHICAGO

OFFICERS FOR 1922-1923

CHAIRMAN

ARNO B. LUCKHARDT - - - - - - CHICAGO

VICE CHAIRMAN

KENNETH M. LYNCH - - - - - DALLAS, TEXAS

SECRETARY

J. J. MOORE - - - - - - - - - CHICAGO

EXECUTIVE COMMITTEE

HOWARD T. KARSNER, CLEVELAND
E. R. LECOUNT, CHICAGO
JOHN A. KOLMER, PHILADELPHIA

Digitized by Google

Digitized by Google

LIST OF OFFICERS

Those named below have served as officers in this section. This branch of the practice of medicine has been included with other subjects in the earlier years, as will be seen by the headings which denote the different section titles. The names of the officers have been taken from the published records, which are deficient in some cases. It will be appreciated if any additional data are brought to the attention of the Secretary of the American Medical Association.

SECTION ON PRACTICAL MEDICINE, MATERIA MEDICA AND PHYSIOLOGY

1873 Chairman, N. S. Davis, Chicago.
Secretary, G. E. Frothingham, Ann Arbor, Mich.

1874 Chairman, Austin Flint, Sr., New York.
Secretary, J. K. Bartlett, Milwaukee.

1875 Chairman, F. G. Smith, Philadelphia.
Secretary, B. A. Vaughan, Columbus, Miss.

1876 Chairman, P. G. Robinson, St. Louis.
Secretary, B. A. Vaughan, Columbus, Miss.

1877 Chairman, A. L. Loomis, New York.
Secretary, J. H. Etheridge, Chicago.

1878 Chairman, T. F. Rochester, Buffalo.
Secretary, W. C. Glasgow, St. Louis.

1879 Chairman, J. S. Lynch, Baltimore.
Secretary, W. C. Glasgow, St. Louis.

1880 Chairman, William Pepper, Philadelphia.
Secretary, T. A. Ashby, Baltimore.

1881 Chairman, J. A. Ochterlony, Louisville, Ky.
Secretary, D. J. Roberts, Nashville, Tenn.

1882 Chairman, J. H. Hollister, Chicago.
Secretary, J. G. Lee, Pennsylvania.

1883 Chairman, J. V. Shoemaker, Philadelphia.
Secretary, W. C. Wile, Sandy Hook, Conn.

1884 Chairman, H. D. Didama, Syracuse, N. Y.
Secretary, G. M. Garland, Boston.

1885 Chairman, J. T. Whittaker, Cincinnati.
Secretary, B. L. Coleman, Frankfort, Ky.

1886 Chairman, J. S. Lynch, Baltimore.
Secretary, J. B. Marvin, Louisville, Ky.

1887 Chairman, A. B. Palmer, Ann Arbor, Mich.
Secretary, N. S. Davis, Jr., Chicago.

1888 Chairman, F. C. Shattuck, Boston.
Secretary, G. A. Backler, Cincinnati.

1889 Chairman, J. H. Musser, Philadelphia.
Secretary, H. M. McColl, Lapeer, Mich.

1890 Chairman, B. A. Vaughan, Columbus, Miss.
Secretary, George Dock, Galveston, Texas.

SECTION ON PRACTICE OF MEDICINE AND PHYSIOLOGY

1891 Chairman, R. T. Edes, Washington, D. C.
Secretary, J. M. French, Cincinnati.

SECTION ON PHYSIOLOGY AND DIETETICS

1892 Chairman, C. H. A. Kleinschmidt, Washington, D. C.
Secretary, Ephraim Cutter, New York.

1893 Chairman, I. N. Love, St. Louis.
Secretary, Ephraim Cutter, New York.

Digitized by Google

LIST OF OFFICERS—Continued

1894 Chairman, E. H. Woolsey, Oakland, Calif.
Secretary, C. G. Chaddock, St. Louis.

1895 Chairman, H. Bert Ellis, Los Angeles.
Secretary, H. Salzer, Baltimore.

1896 Chairman, A. P. Clark, Boston.
Secretary, Ephraim Cutter, New York.

1897 Chairman, Randall Hunt, Shreveport, La.
Secretary, A. H. Tuttle, Boston.

1898 Chairman, J. Weir, Jr., Owensboro, Ky.
Secretary, Lee Kahn, Leadville, Colo.

1899 Chairman, Elmer Lee, New York.
Secretary, R. Harvey Cook, Oxford, Ohio.

SECTION ON PATHOLOGY AND BACTERIOLOGY

1900 Chairman, L. Hektoen, Chicago.
Secretary, F. B. Wynn, Indianapolis.

SECTION ON PATHOLOGY AND PHYSIOLOGY

1901 Chairman, F. B. Wynn, Indianapolis.
Secretary, J. McFarland, Philadelphia.
Delegate, W. A. Evans, Chicago.

1902 Chairman, Victor C. Vaughan, Ann Arbor, Mich
Secretary, J. McFarland, Philadelphia.
Delegate, E. R. LeCount, Chicago.

1903 Chairman, J. McFarland, Philadelphia.
Secretary, H. A. Christian, Boston.
Delegate, A. P. Ohlmacher, Detroit.

1904 Chairman, Winfield S. Hall, Chicago.
Secretary, H. A. Christian, Boston.
Delegate, J. McFarland, Philadelphia.

1905 Chairman, H. A. Christian, Boston.
Secretary, Walter L. Bierring, Iowa City.
Delegate, J. McFarland, Philadelphia.

1906 Chairman, Walter L. Bierring, Iowa City.
Secretary, Walter B. Cannon, Boston.
Delegate, Winfield S. Hall, Chicago.

1907 Chairman, Walter B. Cannon, Boston.
Secretary, M. J. Rosenau, Washington, D. C.
Delegate, W. M. L. Coplin, Philadelphia.

1908 Chairman, M. J. Rosenau, Washington, D. C.
Secretary, H. Gideon Wells, Chicago.
Delegate, H. A. Christian, Boston.

1909 Chairman, H. Gideon Wells, Chicago.
Secretary, Yandell Henderson, New Haven, Conn.
Delegate, Walter B. Cannon, Boston.

1910 Chairman, Yandell Henderson, New Haven, Conn.
Secretary, Leo. Loeb, St. Louis.
Delegate, Walter L. Bierring, Iowa City.

1911 Chairman, Leo Loeb, St. Louis.
Vice Chairman, William Ophüls, San Francisco.
Secretary, A. W. Hewlett, Ann Arbor, Mich.
Delegate, E. R. LeCount, Chicago.

1912 Chairman, A. W. Hewlett, Ann Arbor, Mich.
Vice Chairman, A. J. Carlson, Chicago.
Secretary, William Ophüls, San Francisco.
Delegate, Yandell Henderson, New Haven, Conn.

1913 Chairman, William Ophüls, San Francisco.
Vice Chairman, L. B. Wilson, Rochester, Minn.
Secretary, A. J. Carlson, Chicago.
Delegate, Richard M. Pearce, Philadelphia.

1914 Chairman, A. J. Carlson, Chicago.
Vice Chairman, L. B. Wilson, Rochester, Minn.
Secretary, Frederick P. Gay, Berkeley, Calif.
Delegate, A. W. Hewlett, Ann Arbor, Mich.

Digitized by Google

LIST OF OFFICERS—Continued

1915 Chairman, Frederick P. Gay, Berkeley, Calif.
Vice Chairman, James Ewing, New York.
Secretary, Isabella C. Herb, Chicago.
Delegate, A. W. Hewlett, Ann Arbor, Mich.

1916 Chairman, James Ewing, New York.
Vice Chairman, C. W. Green, Columbia, Mo.
Secretary, Isabella C. Herb, Chicago.
Delegate, H. Gideon Wells, Chicago.

1917 Chairman, Louis B. Wilson, Rochester, Minn.
Vice Chairman, Francis Carter Wood, New York.
Secretary, Isabella C. Herb, Chicago.

1918 Chairman, Francis Carter Wood, New York.
Vice Chairman, Isabella C. Herb, Chicago.
Secretary, J. J. Moore, Chicago.
Delegate, E. R. LeCount, Chicago.

1919 Chairman, Howard T. Karsner, Cleveland.
Secretary, J. J. Moore, Chicago.
Delegate, E. R. LeCount, Chicago.

1920 Chairman, E. R. LeCount, Chicago.
Vice Chairman, William S. Carter, Galveston, Texas.
Secretary, J. J. Moore, Chicago.
Delegate, James Ewing, New York.

1921 Chairman, John A. Kolmer, Philadelphia.
Secretary, J. J. Moore, Chicago.
Delegate, D. J. Davis, Chicago.

1922 Chairman, Arno B. Luckhardt, Chicago.
Vice Chairman, Kenneth M. Lynch, Dallas, Texas.
Secretary, J. J. Moore, Chicago.
Delegate, D. J. Davis, Chicago.

Digitized by Google

Digitized by Google

CONTENTS

	PAGE
List of Officers	7
Proceedings of the Section	13
Chairman's Address: State Licensure Applied to Laboratorians. John A. Kolmer	17
Standardization of Clinical Laboratories. Josiah J. Moore	24
The Intestinal Rate and the Form of the Feces. Francis Lowell Burnett	38
Does Cancer Arise in Chronic Gastric Ulcer? William Carpenter MacCarty	45
Acute Dilatation of the Stomach. Lester R. Dragstedt and Carl A. Dragstedt	51
Pulmonary Aspiration of Particulate Matter, Normally and During Anesthesia. H. J. Corper	64
Studies on the Relation of the Thyroid to Pancreatic Diabetes in Dogs, with Suggestions as to Diabetes Mellitus in Man. Gedide A. Friedman and Julius Gottesman	79
Pneumococcus Antibody Solutions Specific Against Types I, II and III. F. M. Huntoon	102
Production of Arteriosclerosis in Rabbits by Diets Rich in Animal Proteins. L. H. Newburgh and Sarah Clarkson	113
The Congenital Factor in Chronic Renal Disease. Edward Weiss	120
Some Recent Additions to the Knowledge of Ascariasis. B. H. Ransom	127
Cultivation of Trichomonas, and the Question of Differentiation of the Flagellates. Kenneth M. Lynch	138
Endocrinology. Lewellys F. Barker	148
Some Conditions Controlling Internal Secretion. W. B. Cannon	158
The Relation of the Internal Secretions to Metabolism. Joseph C. Aub	171
Hypofunction and Hyperfunction of the Ductless Glands. A. J. Carlson	180
Some Principles of Endocrinology Applicable to Organotherapy. R. G. Hoskins	204
Index	221

Digitized by Google

Digitized by Google

PROCEEDINGS OF THE SECTION

WEDNESDAY, MAY 24—AFTERNOON

The meeting was called to order at 2:15 by the chairman, Dr. John A. Kolmer, Philadelphia.

Drs. Frank M. Huntoon, Swarthmore, Pa., and C. C. Bass, New Orleans, were appointed to serve on the Executive Committee.

Dr. John A. Kolmer, Philadelphia, read the chairman's address, entitled, "State Licensure Applied to Technicians."

Dr. Josiah J. Moore, Chicago, read a paper on "Standardization of Clinical Laboratories."

These two papers were discussed by Drs. Fred I. Lackenbach, San Francisco; Philip Hillkowitz, Denver; C. C. Bass, New Orleans; Frank M. Huntoon, Swarthmore, Pa.; Ward Burdick, Denver; Herman Spitz, Nashville, Tenn.; A. J. Carlson, Chicago; J. H. Black, Dallas, Texas, and Josiah J. Moore, Chicago.

Dr. J. H. Black, Dallas, Texas, made a motion that a committee of three be appointed by the chairman to go over Dr. Moore's paper as to the feasibility of the plan for the standardization of laboratories and to bring in a report. Seconded and carried.

Drs. C. C. Bass, New Orleans; Kenneth Lynch, Dallas, Texas, and Philip Hillkowitz, Denver, were appointed and instructed to report Thursday afternoon.

The resolution referred to in the minutes of the Section on Practice of Medicine was offered, and, after discussion, was adopted.

Dr. Francis Lowell Burnett, Boston, read a paper on "Intestinal Rate and the Form of the Feces." No discussion.

The President, Dr. George E. de Schweinitz, and the retiring President, Dr. Hubert Work, addressed the section.

Dr. William Carpenter MacCarty, Rochester, Minn., read a paper on "Does Cancer Arise in Gastric Ulcer?" Discussed by Drs. Herbert R. Brown, Rochester, N. Y.; John J. Gilbride, Philadelphia; J. Shelton Horsley, Richmond, Va.; Philip Hillkowitz, Denver; William H. Stewart, New York; D. J. Davis, Chicago; Eugene L. Opie, St. Louis, and William Carpenter MacCarty, Rochester, Minn.

Dr. Lester Dragstedt, Chicago, read a paper on "Acute Dilatation of Stomach." Discussed by Drs. James J. Moorhead, Terre Haute, Ind.; John J. Gilbride, Philadelphia; A. J. Carlson, Chicago, and Lester Dragstedt, Chicago.

Digitized by Google

Dr. Harry J. Corper, Denver, read a paper on "Pulmonary Aspiration of Particulate Matter Normally and During Anesthesia." No discussion.

Drs. G. A. Friedman and Julius Gottesman, New York, presented a paper on "A Study on the Relation of the Thyroid to the Pancreatic Diabetes in Dogs." Discussed by Drs. Walter M. Boothby, Rochester, Minn.; Charles W. Greene, Columbia, Mo.; Arno B. Luckhardt, Chicago; A. J. Carlson, Chicago, and G. A. Friedman, New York.

Thursday, May 25—Afternoon

The meeting was called to order at 2 o'clock by the chairman.

The following officers were elected: chairman, Dr. Arno B. Luckhardt, Chicago; vice chairman, Dr. Kenneth M. Lynch, Dallas, Texas; secretary, Josiah J. Moore, Chicago; delegate, Dr. D. J. Davis, Chicago; alternate, Dr. John A. Kolmer, Philadelphia.

Dr. Frank M. Huntoon, Swarthmore, Pa., read a paper on "Pneumococcus Antibody Solutions Specific Against Types I, II and III." Discussed by Drs. John A. Murphy, Swarthmore, Pa., and John A. Kolmer, Philadelphia.

The Committee on Standardization of Laboratories, Dr. C. C. Bass, chairman, made the following report:

> The committee finds itself unable to make recommendations as to the adoption of the proposition at the present time on account of the importance of the subject, which it is believed requires extended study.
>
> The committee does recommend that a committee be appointed to consider the matter and make recommendations at the next session of the Association.

It was moved and carried that this report be received and put into effect.

The chairman appointed the same committee to serve during the coming year and to submit a further report at the coming meeting.

Dr. Lloyd J. Thompson, Boston, introduced the resolution on the standardization of the Wassermann test, referred to in the minutes of the Section on Urology.

Dr. Kenneth M. Lynch, Dallas, Texas, moved that this resolution be adopted by the section and that Dr. John A. Kolmer be appointed as a committee of one to cooperate with like committees representing the Sections on Urology, Dermatology, Syphilology, Practice of Medicine, and Nervous and Mental Diseases. Unanimously carried.

Dr. L. H. Newburgh, Ann Arbor, Mich., read a paper on "The Production of Arteriosclerosis in Rabbits Caused by Feeding Diets Rich in Animal Proteins." Discussed by Drs. M. W. Lyon, Jr., South Bend, Ind., and L. H. Newburgh, Ann Arbor, Mich.

Digitized by Google

Dr. Edward Weiss, Philadelphia, read a paper on "The Congenital Factor in Chronic Renal Disease." No discussion.

Dr. Edwin R. Le Count, Chicago, read a paper on "Discussion of Secondary Hemorrhages in the Brain." Discussed by Drs. M. W. Lyon, Jr., South Bend, Ind.; William House, Portland, Ore.; John A. Kolmer, Philadelphia, and Edwin R. Le Count, Chicago.

Dr. M. A. Mortensen, Battle Creek, Mich., read a paper on "Diagnosis and Pathologic Physiology of Beginning Myocardial Inefficiency." No discussion.

Dr. Kenneth M. Lynch, Dallas, Texas, read a paper on "Cultivation of Trichomonas and the Question of Specific Differentiation." Discussed by Drs. John A. Kolmer, Philadelphia, and Kenneth M. Lynch, Dallas, Texas.

Dr. B. H. Ransom, Washington, D. C., read a paper on "Recent Additions to the Knowledge of Ascariasis."

Digitized by Google

Digitized by Google

STATE LICENSURE APPLIED TO LABORATORIANS *

JOHN A. KOLMER, M.D. D.Sc.
Professor of Pathology and Bacteriology, Graduate School of Medicine of the University of Pennsylvania
PHILADELPHIA

A progressive development of laboratory methods for the study and diagnosis of disease and a rapid multiplication of hospitals, diagnostic clinics and laboratories, have created a constantly increasing demand for laboratorians. More and more, physicians and surgeons are demanding accurate and reliable pathologic, bacteriologic, serologic and chemical examinations and the preparation of biologic products, as diagnostic aids and therapeutic measures.

The number of medical graduates of sufficient special training in laboratory medicine adopting the laboratory as a career and specialty is inadequate to meet this demand. Graduates in medicine are not being attracted to laboratory careers in sufficient numbers, largely because of inadequate financial compensation and limited opportunities for advancement. As a result, it is becoming increasingly difficult to provide instructors in the medical sciences for medical schools, and heads for large hospital and municipal laboratories. It is imperative that salaries shall be revised upward, and that teachers of pathology and bacteriology in medical schools shall renew their efforts to attract students and recent graduates to laboratory careers. This can be done largely by developing and encouraging those who show special aptitude and leaning toward this work.

One result of the increasing demand for laboratorians and the shortage of medical graduates adopting

* Chairman's Address.

Digitized by Google

this work has been an increase in the number of lay persons engaging in medical laboratory practice. In some instances, these are doctors of philosophy who have majored in the medical sciences, and doctors of public hygiene or certified sanitarians with special training in laboratory medicine, but not infrequently they are technicians, trained more or less thoroughly in laboratory methods and varying greatly in experience, skill and personal fitness.

In my opinion, it is indeed fortunate that properly prepared lay persons are attracted to laboratory careers. So far as clinicopathologic, bacteriologic, serologic and chemical work are concerned, there is no reason why doctors of philosophy or public hygiene, and experienced laboratory technicians who have given these subjects special study and attention, should not qualify and prove as capable for conducting the examinations as the medical graduate, and, indeed, prove more efficient, in comparison, if the latter has nothing more than the usual undergraduate medical courses of instruction in the way of technical training and experience. In other words, a course in medicine is not essential in preparation for the technical side of this work. But a medical education and experience are required in preparation for independent work in tissue pathology and roentgenology.

However, for the interpretation of laboratory examinations, a medical education is essential. For this reason, the directors or heads of medical laboratories should be graduates of medicine, possessing a fair degree of clinical experience in order that they may serve as consultants in this field for evaluating the results of laboratory examinations and may aid the physician and surgeon in correlating them with clinical data. In other words, a medical education would appear essential in preparation for the highest positions in medical laboratories, and the interpretation of examinations in tissue pathology, serology (with special

Digitized by Google

reference to the Wassermann reaction) and roentgenology should always be in the hands of the specially trained and experienced graduate in medicine.

Unquestionably, properly trained and careful technicians can conduct the various tests and examinations in clinical pathology, bacteriology, chemistry and serology and prepare sections of tissue, as well as medically trained pathologists can. In fact, women are usually endowed by nature with more patience and aptitude for details than the average man and are more likely to be content with routine work. When especially trained in a certain branch instead of being required to have a smattering of all kinds of laboratory methods, they are capable of rendering very satisfactory services and are fast becoming as indispensable for the conduct of medical laboratories as nurses are in the practice of medicine and surgery.

In a large number of institutions, technicians are being practically depended on for the conduct of laboratories, with little or no supervision. In some instances, commercial laboratories are being conducted by them, and the patronage of physicians and sometimes of the laity is being solicited. With the smaller hospitals, there appears no alternative, as the work does not enable the institution to pay an adequate salary for a well-trained pathologist, although much could be done by employing a pathologist to serve part time in two hospital laboratories overseeing and directing the work of the laboratory interns and technicians.

For various reasons, therefore, nonmedical persons in increasing numbers are engaging in medical laboratory practice. So far as making tests and examinations are concerned, nonmedical graduates and technicians possessing adequate training and experience are as acceptable as medical graduates; but, in tissue pathology, a medical education is essential, as it is likewise for the interpretation of laboratory results in general, with special reference to tissue pathology, serology and roentgenology. The question now arises

Digitized by Google

regarding the legal status of nonmedical laboratorians in relation to the laws governing the practice of medicine in the different states; also as to whether or not it is advisable for state boards of medical licensure to devise some means of bringing nonmedical laboratorians under control, especially those conducting laboratories without the supervision of a doctor of medicine, who may be held responsible.

In a broad and general manner, persons making medical laboratory tests and examinations and reporting the results of these to physicians are engaged in the practice of medicine, even though they do not apply remedial measures. When bacteriologic examinations are made and an autogenous vaccine is prepared, with advice for the physician as to dosage, the technician comes even closer to the actual practice of medicine, even though he or she may not actually give the injections. The practice of medicine cannot be construed as being confined to the application of remedies; laboratory examinations are properly included, since the results may be applied in the making of diagnoses and the application of remedial measures. A recent decision by Attorney-General Allen [1] of Massachusetts was to the effect that "a person acting as a pathologist should be registered under the law providing for medical registration." In this particular case, the acting pathologist was a doctor of medicine who did not believe that registration was required for conducting pathologic work. The decision opens up the probability that other laboratorians must secure registration in Massachusetts and other states with similar laws; as stated by Allen: "In order to practice medicine one need not cover the entire field of the science. If he devotes himself to a very restricted part of it, he still may be found to practice medicine. It is a matter of common knowledge that there has been great specialization in the profession in recent years."

1. Boston M. & S. J. **87**: 186 (Jan. 19) 1922.

Digitized by Google

According to this opinion, a doctor of medicine who is confining his or her work to the laboratory, under the broad and general designation of "pathologist," is engaged in the practice of medicine and must be registered to avoid the possibility of prosecution. But how about the doctors of philosophy and the non-degree technicians who, in many instances, are conducting medical laboratories without the supervision of a registered doctor of medicine to assume responsibility? Is it not a matter of importance that the state shall inquire into their qualifications for conducting a medical laboratory and insist on a minimum standard of education, skill and experience in this work? What is the medicolegal status of their examinations—for example, the results of a Wassermann test in a divorce suit?

Should the states provide for the examination and registration of nonmedical laboratorians? Or would it suffice for the states to require that they practice only under the supervision of a medical graduate laboratorian who assumes responsibility? Or is it sufficient to let matters stand as at present, in which case physicians and laity shift for themselves in having pathologic, bacteriologic, serologic, chemical and even roentgenologic examinations made by any one whom they select or may be compelled by circumstances to call on, whether or not they are medical graduates and regardless of their qualifications in general?

Opinions on these questions may vary considerably. As long as nonmedical laboratories make examinations and submit reports to physicians only, it may be granted that the latter assumes most of the responsibility and that it makes little difference to the state whom the physician calls on for these examinations and for even the interpretation of the results. Under these conditions, the state may claim to afford ample protection to her citizens by holding physicians responsible, provided nonmedical and unregistered laboratories are forbidden to make medical examinations for the laity.

Digitized by Google

However, it is inconsistent to require examination and registration of medical graduates specializing in laboratory medicine and allow all other laboratorians doing similar work to practice without fulfilling these requirements, as is the case at the present time. Nothing need nor should be done to prevent nonmedical laboratorians from engaging in this work, because the majority are capable of conducting laboratory examinations in a thoroughly acceptable manner, and their services are invaluable and indispensable; but nonmedical laboratorians should not be permitted to interpret the result of examinations to the laity, because this touches on the diagnosis and possibly on the treatment of disease and so involves the practice of medicine. Under these conditions, a nonmedical laboratorian could examine the urine of a person and even make a Wassermann test for him, but the results should be interpreted by a physician, unless the individual wishes to rely on his own judgment and information.

I believe that the time has arrived when the state should give these questions some attention, in reference not only to medical laboratory examinations but also to the roentgenologic work being done by nonmedical technicians.[2] Many physicians—probably the majority—give little or no attention to the qualifications of those to whom their laboratory work is entrusted. During former days, when most clinical laboratory work embraced simple urine and blood examinations, errors probably did little harm, but the chances of harm resulting from erroneous Wassermann reactions, tissue diagnoses and various bacteriologic and chemical examinations may be considerable, and, indeed, with the Wassermann reaction, may be incalculable, in relation to the domestic life, health and happiness of the patients. As a general rule, practicing physicians do not realize the many chances for error in laboratory

2. Trostler, I. S.; Darling, B. C., and Landau, G. M.: Medical Supervision of Commercial Laboratories, J. A. M. A. **78**: 1219 (April 22) 1922.

Digitized by Google

work; "to them a test is a test, regardless of by whom or how it is made;" and not a few fail to realize the necessity for skill, experience and care for the proper conduct of most medical laboratory examinations.

While individual rights against state interference and control are to be carefully guarded, some means should be found by the state for the licensure and control of nonmedical laboratorians engaging in general laboratory work without medical supervision; just as the state may require the examination and licensure of the doctor of medicine practicing pathology, in a general sense, as a specialty. The technician employed in a physician's office and the technicians working in an institutional laboratory under a licensed physician would be untouched, as the physician or institution may be trusted with passing on the qualifications of the technician and assumes responsibility for his or her work. But provision should be made for the examination and licensure of the doctors of philosophy and hygiene and other technicians who are not doctors of medicine, who are engaging in independent medical laboratory work and practice either in commercial, municipal or institutional laboratories. So many nongraduates of medicine are entering on medical laboratory practice that some regulation and some acceptable criteria of fitness for this work are required for the protection of both the medical profession and the laity, and especially so, since medical laboratory examinations are being requested and relied on more and more as aids in the diagnosis and treatment of disease.

Digitized by Google

STANDARDIZATION OF CLINICAL LABORATORIES

JOSIAH J. MOORE, M.D.
Director National Pathological Laboratory
CHICAGO

Although the classification of medical schools has raised the level of medical education of the undergraduates and also improved the present status of graduate and postgraduate schools, the majority of physicians, for various reasons, rely on clinical laboratories for much of their diagnostic laboratory work and for much of the newer knowledge in medicine. The pathologist is rapidly advancing from being a good or poor technician to a consultant who must not only be expert in his own line, but in addition must have considerable knowledge of all the specialties. In order to have this information, the training must be broad in actual experience and practical skill.

The ideal laboratory director should be a broad minded, conservative, conscientious pathologist, preferably with clinical training, who must give freely of his knowledge to that group of physicians who depend on him for laboratory service. His rôle should be that of adviser and consultant, and he should be directly interested in having individual physicians or the profession as a unit acquainted with the value of the more accurate modern procedures of his specialty.

The average practitioner has four methods of keeping up with his education: (1) through clinics and postgraduate courses; (2) through the literature; (3) through teaching in medical colleges, and (4) through laboratory connections. Not all find it possible to take the first. We know by statistics and by the number of unopened journals on the desks of

Digitized by Google

too many physicians that the second is not infrequently neglected. And only a few of those who live in cities where medical colleges are located can learn through teaching. But every practitioner at the present time should, and, I believe, does make some use of the clinical laboratory. The tests are so numerous that every physician at some time or other must come in contact with laboratory men. Here lies the greatest opportunity for the laboratory to give full service to the profession. Here is one of the strongest reasons for keeping laboratories up to a certain standard.

To reach the highest efficiency, laboratories should have in their personnel men and women of the same type as those found in medical colleges and research institutions. Medical colleges and hospitals are appreciating this, and a gradually increasing number of teaching pathologists are acting as directors of the laboratories of affiliated hospitals. This in most instances works out satisfactorily to both the school and the hospital, and is certainly a potent factor in the maintenance of efficient clinical laboratory work.

The time is past when a physician who is unsuccessful as a practitioner can start a laboratory as a last resort. Too many mistakes are made by this plan. I feel sure that most surgeons would prefer that all tissues removed by them should be examined and reported on by trained pathologists, rather than to trust to neophytes who have had a six weeks' course. Numerous mistakes in tissue diagnosis have occurred and will occur through such inexperience. It is now the custom of the majority of large hospitals to have full-time pathologists as directors of their laboratories rather than to have interns acting as pathologists. This has also made it advisable for laboratories unable to secure experienced pathologists to employ larger laboratories or teaching pathologists as consultants.

There is probably no laboratory test in which more mistakes are made than in the Wassermann reaction.

Digitized by Google

Efforts to render this test as reliable as modern procedures will permit by a standardized technic and standardized antigens have been attempted in Europe and this country. I feel that Kolmer [1] has done effective work in his exhaustive study of the numerous technical methods and in his presentation of a standard method. This was not brought forth to stop investigative study of the Wassermann reaction, which still remains unexplained, but to protect the patient and the physician from errors due to faulty technic and wrong interpretations in the hands of the laboratory technician. If it succeeds in this, Kolmer will have accomplished much. A similar attitude is manifested by the New York Department of Health,[2] which says: "The complement fixation test for the diagnosis of syphilis shall be attempted only by those who are especially trained and qualified to do the work. It is undesirable for a laboratory to undertake the performance of the complement fixation test for syphilis unless the number of specimens examined is sufficient to insure adequate control of the reagents and methods used." Both statements are especially appropriate, the first in the fact that large numbers of courses of from two to four weeks are given in the Wassermann technic; and secondly, in the desire of many small hospitals with but few Wassermann tests to have them made in their own laboratory by a young woman who must, in addition, pose as an expert bacteriologist and blood chemist, and do all the routine work in the laboratory, besides taking an occasional roentgenogram. In addition to making the tests, she must also interpret the results—which, combined with little medical knowledge on the part of the technician and no medical supervision, often leads to disastrous complications.

Writing on an allied subject, the Committee on Radiological Frauds and Improper Practices of the

1. Kolmer, J. A.: Am. J. Syph. 6: 82 (Jan.) 1922.
2. Laboratory Manual, New York State Department of Health, 1920, p. 20.

Digitized by Google

Radiological Society of North America [3] states that:

In May, 1921, the following resolution was passed by the Comitia Minora of the Medical Society of the County of New York:

"As a matter of public policy, it is recommended to the profession that their support of commercial laboratories be withdrawn, and wherever possible, patients be referred to laboratories under the supervision of competent and qualified medical men."

A lay technician who opens his own office and works entirely independent of medical supervision is violating the medical practice act when he gives out written and verbal diagnosis of pathologic conditions, in that he is practicing medicine without a license.

In order that there might be a definite plan to work on, a set of requirements for laboratories was prepared and submitted to a large number of laboratory directors and pathologists, and from the comments and suggestions which they made the following may be submitted:

GENERAL STANDARD REQUIREMENTS FOR CLINICAL LABORATORIES

1. The director of a clinical laboratory should be a medical graduate.

2. All interpretations of laboratory data should be made by doctors (of medicine, philosophy or public health) who are specialists in the branch of work to which the data pertain, i. e.:

(*a*) Serologic, bacteriologic and chemical interpretations should be made by doctors who are trained serologists, bacteriologists and chemists.

(*b*) Tissue diagnosis should be made by doctors of medicine who are experienced pathologists.

3. Technical procedures (methods) used in an acceptable laboratory should be the best available: those used and approved by authorities.

4. The equipment of an acceptable laboratory should be such that the proper technical procedures may be

3. Trostler, I. S.; Darling, B. C., and Landau, G. M.: Medical Supervision of Commercial Laboratories, J. A. M. A. 78: 1219 (April 22) 1922.

Digitized by Google

carried out. There should be ready access to current scientific books and journals.

COMMENT

With reference to these suggested requirements, the following statement is made:

1. The director of a laboratory should be able to act as consultant in evaluating for his clients the various laboratory reports and in correlating them and other clinical data.

2. Many technical methods—most of them, perhaps—may be satisfactorily carried out by technicians. The data derived by such methods, however, should be interpreted by specialists.

3. If it is insisted that only the best modern methods be used in a laboratory, it follows that the technicians employed must be trained in these methods.

4. Clinical data and other pertinent information should accompany the submission of specimens or other material to the laboratory.

The scarcity of medical graduates with proper training in laboratory work has led to the suggestion that the director of the laboratory may be a doctor of philosophy who has specialized in bacteriology, medical parasitology, serology or allied subjects, or a doctor of public health. These may, when necessity arises, have access to medical consultation. In discussing this subject, the Laboratory Manual of the New York State Department of Health [2] states that "directors of laboratories, approved for these examinations (i. e., for the diagnosis of diphtheria, tuberculosis, typhoid fever and other communicable diseases) should preferably be graduates of medicine, or bacteriologists of sufficient education and experience to interpret the significance of the results of laboratory examinations. Members of the staff who make diagnoses shall have trained under qualified experts and shall have not less than one year's experience in a bacteriologic laboratory."

Digitized by Google

Dr. Wadsworth, director of the New York State Department of Health Laboratories, says in a personal communication that:

> It has been so difficult to secure graduates in medicine who are also qualified in laboratory work that competent bacteriologists and serologists without a medical education have been accepted. They have often proved more efficient. In all our work we try to avoid making diagnoses, reporting simply the results of the examinations, leaving diagnosis entirely in the hands of the physician at the bedside.

Since it is suggested that the director should be able to act as a consultant, it necessarily follows that the medical graduate is best qualified. Secondly, there is entire accord that tissue diagnosis should be made by doctors of medicine who are experienced pathologists. It does not necessarily follow that the pathologist should be director of the laboratory; but such a combination gives, in my opinion, the most happy results. The question has arisen whether it is not the function of the physician in charge of the patient to evaluate the laboratory report and interpret it with the clinical data. This opinion is perfectly sound, but one difficulty comes from the fact that many practicing physicians cannot evaluate the newer laboratory examination; and if the laboratory reports are made by technicians, no matter how skilled, the laboratory and the patient will fail to get the best results. Various methods for standardizing clinical laboratories may be proposed. An illustration of public health laboratory standardization is to be found in New York. In a brief description of the method employed here, Wadsworth [4] says that the first step was made when the sanitary code established by the public health council of the state, under legislative authority, prescribed that certain diagnostic examinations must be made in a laboratory approved by the commissioner of health. Such examinations, when made in other laboratories, thus have

4. Wadsworth, A. B.: Cooperation Between a Central State Laboratory and Local Municipal and County Laboratories, J. A. M. A. 77: 512 (Aug. 13) 1921.

Digitized by Google

no standing in court. Later the laws were amplified to require that laboratories engaged in public health work secure the approval of the commissioner of health. Approved laboratories must adopt prescribed methods of examination, and a uniform system of reporting and of keeping records. They are occasionally inspected by authorized representatives of the commissioner of health, who advise persons in charge as to methods employed, and are frequently sent test specimens from the central laboratory for checking up on their work. The laboratories are approved for one year. A manual [2] is issued which gives in detail standard methods of procedure for performing the various examinations. Dr. Wadsworth states that such a standard requirement as that submitted is an important step toward standardization, but it is difficult to understand how results are to be obtained unless there is definite responsibility fixed upon some official agency for the supervision and practical testing of the work of the laboratories. It has been necessary in New York State not only to formulate standards, but also to determine the fact that these standards are actually maintained by inspection tests at stated intervals.

Such a method of state control of public health laboratories could be adopted in each state, but there would surely arise the same difficulties we now have with the multiplication of state boards of medical examiners. Many laboratories could also exist by this plan without approval and control. The state board of medical examiners of Pennsylvania, which has under its jurisdiction the approval and standardization of hospitals for interns, requires minimum standards of laboratory equipment and a competent personnel for the hospital laboratory, which is a progressive step in the proper direction.

A more general system of supervision appears desirable, and this may be accomplished by having the

Digitized by Google

Hygienic Laboratory of the United States Health Service act as the central authorized body. This would be somewhat similar to the issuing of licenses to biologic laboratories for the sale of their products in interstate commerce. Here again we would have difficulties, since the majority of laboratories do work only for a community or local area within the state, and there might arise questions of state and national rights.

In the rapid advance of medical education in this country, the rapid rise in the standard of the medical colleges was accomplished by the colleges themselves in the Association of American Medical Colleges, and the Council on Medical Education and Hospitals of the American Medical Association. It may be possible for the clinical laboratories to form an association and achieve the same success. However, one attempt of this kind has already been made, and the results were not encouraging. The large number of laboratories, in connection with hospitals and private institutions, makes such an undertaking difficult unless strongly supported by some stronger and older organization, such as the American Medical Association.

Another organization, the American College of Surgeons, has undertaken standardization of hospitals, and the Council on Medical Education and Hospitals of the American Medical Association has listed the requirements for institutions offering services to interns. Since the minimum standard requirements for hospitals as stipulated contain clauses applicable to clinical and roentgen-ray laboratories, it may be possible that such clauses may be enlarged to cover the details of the minimum requirements herein set forth.

The support of the American Medical Association, the American College of Surgeons, the Hygienic Laboratory of the United States Public Health Service and the proposed Association of Clinical Laboratories for the enforcement of such a standard of requirements for clinical laboratories as suggested in this paper, or

Digitized by Google

a satisfactory modification of such a standard, is necessary in order to insure the complete attainment of this plan. Such a plan in successful operation would be comparable to a raising of the standard of medical education, as a progressive step in the advancement of medical science.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. KOLMER AND MOORE

DR. FRED I. LACKENBACH, San Francisco: A very valuable means of control is that exercised by the postoffice department. A regulation provides that all specimens sent through the mail shall go into a laboratory, provided the laboratory has a medical director in charge. That matter came up in San Francisco a few years ago. The container of a specimen sent through the mails was broken, and the specimen was scattered. It led to an investigation. The postoffice department sent a man to the various laboratories to find out what conditions were, and provided for issuing permits to these laboratories where the conditions were found acceptable; one of the conditions was that there should be a medical man in charge of the laboratory. One of the great difficulties in laboratories, so-called commercial laboratories, is the competition of inferior laboratories. Men who want to do good work and are capable of doing good work find themselves confronted with many laboratories that are not doing good work, and it lowers the standard; it lowers the compensation that it is possible to derive from the conduct of a laboratory. Further, there is another element, the competition of a physician or group of physicians employing a technician (perhaps some girl who has had a year or so training), putting her in charge of the laboratory work and letting her do the Wassermann tests and other important work. That class of work certainly does not compare favorably with the so-called commercial laboratories taking them as a whole, because commercial laboratories have a reputation at stake, and if they did poor work they could not continue. But in a laboratory where physicians are in charge and work is done slipshod with no one to pass on it it simply goes! That is one of the complications, it seems to me.

DR. PHILIP HILLKOWITZ, Denver: I take issue with some of the suggestions made, although I am heartily in accord with the end in view. In the first place, I take exception to the premise on which I believe both papers are based, namely, to standardize an impersonal institution as understood in the words "clinical laboratory." I desire to emphasize the fact that the great majority of men who are engaged in clinical

Digitized by Google

pathologic work do not consider themselves laboratory men, but practitioners of medicine engaged in a particular specialty. We think it entirely inadvisable, therefore, to standardize the laboratory or to license the technician any more than the laryngologist or the surgeon would want the state to tell him what kind of surgical instruments he should have, or how well the nurses he had working for him should be trained. We think that every man who engages in clinical laboratory work should be responsible for the technic and interpretation of all tests that come to his laboratory. It is his concern to see that the technicians he trains, or gets from the outside, do their work properly. We do not like the term "laboratory" as something apart from the physician who directs it. As regards the motive for licensing technicians on account of the scarcity of trained pathologists: the reward to the medical man who devotes his life to this field is not commensurate with the time, labor and study involved. That is our fault. Physicians expect hospitals to furnish blood counts, Wassermann tests, etc., on the same basis as light and heat. Every one of these tests should be conducted under the supervision and the proper interpretation of a medical man who is entitled to proper compensation for his function as a consultant. I am sure that education of the public will bring about this result. It should bring it about in every community so that pathologists will receive adequate compensation, as do the surgeons, laryngologists or other specialties. With proper valuation of the work of the pathologists, many a young graduate, instead of turning to the more lucrative fields of internal medicine or surgery, will look to pathology for his life work. If we license technicians, it means that the state places its seal of approval on this particular person. The very same question came up with the state boards of health licensing chiropractors and other cults. Where this license was granted, the "irregulars" now perform surgical operations. We shall have the very same thing with technicians. Therefore, let every clinical pathologist be responsible for the competence of the help in his laboratory.

Dr. C. C. Bass, New Orleans: I doubt whether we have reached the time when a nonmedical person should be licensed to perform any medical function, such as laboratory examinations, without the supervision and direction of competent medical men. It is true that if the physician wishes to delegate any part of his duty or of his work to a person who is specially trained to do that particular work, I think that is quite permissible, whether it is laboratory or other work. If he wishes to have a competent person to make laboratory examinations for himself, perfectly well and good. If a hospital wishes to employ a laboratory technician to perform certain of the technical work under the direction of a competent pathologist, it seems to me quite proper; but

Digitized by Google

there should be no such thing as a hospital laboratory, or any other clinical laboratory, making laboratory examinations and reporting thereon except under the direction of competent medically trained men. Such work being done by nonmedical persons without supervision tends to belittle the recognition of the importance of the work of the clinical laboratory. Not only does such work tend to belittle and cheapen the work of the clinical laboratory, but it also tends to prevent the correction of the cause of the present insufficient number of competent laboratory men, namely, insufficient compensation. If a physician's ability to do reliable laboratory work were as well recognized and as well paid for as the other parts of the practice of medicine, there would not be such a shortage of competent physician laboratory workers as exists today. It seems to me, therefore, that it is unwise to license anybody except medically trained men, or women, to practice this specialty any more than any other specialty in medicine.

Dr. Frank M. Huntoon, Glenolden, Pa.: It seems to me that the whole question develops itself on two points: First, to obtain a competent pathologist who is a competent serologist. Where are you going to get a competent pathologist, and who is going to say he is competent? A pathologist can acquire bacteriology and serology. A man of good judgment and common sense can acquire this if he sufficiently applies himself. Technical pathology, however, is a special subject. The pathologist must have a peculiar type of picture memory which enables him to muster up his past experiences at the time he is looking at his slides. The question of deciding whether a tissue growth is malignant, or nonmalignant is a matter of life and death. Now whom are you going to trust with that diagnosis? Certainly not every technician or a nonmedical man? It seems to me that Dr. Kolmer's idea is that the laborer is worthy of his hire, that a man who makes the diagnosis that takes the application of years of knowledge is as worthy of a consultation fee as the internist who sees the outside of the patient and guesses at what goes on in the inside. In regard to the education of the physician who receives the report: Dr. Moore mentioned in his address that you were really forced to make the diagnosis for the physician. If the laboratory man interprets the results of his examination, he is then acting as a consultant and should receive a consultant's fee.

Dr. Ward Burdick, Denver: I am heartily in accord with the remarks of Dr. Huntoon. I do not think we should let the bars down too freely. There are at present too many lay people crowding at the gate to medicine, as evidenced by chiropractors and osteopaths. I do not approve of it. I merely wish to go on record as speaking against licensing lay people and permitting them to conduct laboratories without medical supervision. I think it is entirely wrong, and I

Digitized by Google

believe that that will do more toward keeping first class men out of this field than anything else that could happen. I believe that this is at present one of the reasons why more good men, well qualified men, are not taking up the specialty of clinical pathology.

DR. HERMAN SPITZ, Nashville, Tenn.: I heartily agree with the statements that have been made. This question has been discussed pro and con for the last nine or ten years. It is a constant topic of discussion, and when a number of laboratory men get together, a constant source of irritation. I feel that a large part of the irritation is our own fault. Our professional colleagues come into our office and ask us to train a technician for them in from four to eight weeks; usually some girl who is looking for a job or a relative of the doctor's. They thereby imply that everything we have acquired in eight or ten years of hard work can be acquired by a girl, with or without a high school education, in from four to eight weeks. It is our own fault if we fall into the trap. We should say: "If you want her to do laboratory work, send her to college for from two to four years to learn to do things properly, and after that time you will get some satisfactory results from her work." If the physicians in my community desire to employ a layman to do their work, whether a woman or a male technician, that is their own business, not mine; but when a physician comes to me and wants laboratory work done and I or my technician, whom I have trained for years and in whose ability I have confidence, runs through a piece of work, I render an opinion in the same spirit that a consultant, whether an internist, an aurist or a surgeon, renders an opinion, and I expect a fee. If they are not willing to pay that, they do not get the service. If the case is a charity one, they get the work irrespective of what the circumstances may be. I feel that if we prolong the discussion of licensing laboratories conducted by laymen, we are simply throwing the bars down and admitting to our colleagues that all this work we have been talking about for so many years as being so highly important and necessary to do is not that at all, but can be done by anybody who has taken a four to six weeks' course in anybody's laboratory. I am certainly opposed to any such system.

DR. A. J. CARLSON, Chicago: We examine a specimen of blood for syphilis. The internist asks for our findings. It is either syphilitic or nonsyphilitic. Is that diagnosis? We examine urine specimens for albumin or sugar, and we find them. Is that diagnosis? When it comes to the interpretation of a tumor, the very best men will frequently differ as to whether it is malignant or not. It seems to me that unless we clearly differentiate here what we mean by rendering diagnosis and reporting on facts, we are merely quibbling in saying that the laboratory director at his office desk with

Digitized by Google

the report of the laboratory man before him is a consultant. Unless the director did the laboratory work he does not know whether there was sugar or albumin in the urine, or whether the blood specimen contained spirochetes. So the onus, as I see it, is still the accuracy of the work. The interpretation cannot be made except in connection with the patient, as to how he contracted the malady and what chance he has to survive. Merely passing on the written laboratory report should not be dignified by the term diagnosis or consultation. The important thing there is the accuracy of the laboratory work. Is that specimen of blood syphilitic? This we cannot determine by sitting at our office desks.

Dr. J. H. Black, Dallas, Texas: In regard to Dr. Carlson's statement, I think there is an important clinical difference between the work of the technician and the pathologist. Take one of the examples he gave for instance, the finding of albumin in urine. Any technician may be able to report whether albumin is present or not, but the technician is not able to discuss intelligently with the physician whether it is a transient condition due to excessive exercise, an orthostatic albuminuria due to a lordosis, or an evidence of a true nephritis. The technician may report sugar in the urine, but cannot discuss intelligently with the physician whether it is an alimentary glycosuria, a renal glycosuria or a true diabetes mellitus. That offers a legitimate field which the technician cannot in any sense fill. We must be able to interpret for the physician our findings if he is not in a position to do it himself. The solution is going to come when the clinical pathologist makes the general practitioner see that he can give service that the technician cannot. We are clamoring constantly that we are consultants and not technicians. If we are qualified to render him service, and do render him service which the technician cannot, then we shall have little difficulty with the practitioner in convincing him that we are something that he really needs.

Dr. Josiah J. Moore, Chicago: The statement of Dr. Hillkowitz that laboratory work in a hospital should not be considered in the nature of overhead expense as water, heat, light, etc., and billed as a flat fee is agreeable to pathologists. It is the tendency of hospitals to do this; but until the surgeon and the clinician are placed on the same basis I hardly think it is fair to the pathologist. Since at present it is difficult to obtain competent pathologists for the medical schools, it will be impossible to have them for fifty-bed hospitals. However, the director of a laboratory does not necessarily have to be in the hospital. With a properly trained technician as resident, who can perform the routine work, the more difficult tests can be sent to the director, who may be some miles away. Dr. Carlson raised a question on the meaning of interpretation and diagnosis. Frequently we are asked to interpret a blood count, following which a conver-

Digitized by Google

sation with the physician on the condition of the patient leads to a suggested diagnosis. We are then acting as consultants and not merely as technicians. Similarly, when making a diagnosis of a specimen of tissue after receiving a complete history or conversing with the surgeon, we are performing our work as consultants. Interpretations are commonly called for in the field of blood chemistry. As far as can be determined, this is now taught only as optional courses in the fourth year of medicine, and the majority of students at present graduate with but little practical knowledge of the subject. Naturally, the graduate of former years is still more handicapped, and here we find a large field for the laboratory man to help both the physician and through him the patient. Whether the laboratory man is a pathologist in a school, in a hospital or in a public clinical laboratory, he should always be a teacher, and that is the kind of men we want in our laboratories.

Digitized by Google

THE INTESTINAL RATE AND THE FORM OF THE FECES *

FRANCIS LOWELL BURNETT, M.D.
BOSTON

A measure of time on the circulatory and respiratory systems has been established for many years and has been found useful. The pulse beat and the respiratory rate are of value not only in the determination, but also in the consideration of the outcome of morbid processes. The intestinal rate, however, has received only scant consideration; but as the tissues of the body are dependent on the amount and kind of assimilation, which is due to the proper chemical reduction, which in turn is nicely adapted to the rate of passage through the different parts of the tube,[1] an understanding of the variations of the intestinal rate and the form of the feces is likely to prove valuable in the most essential process—proper nourishment—and the maintenance of a harmonious body.

The study previously given to the time taken by substances to pass through the alimentary tract has been in attempts to define the normal rate; but the results have been so at variance that they are without practical value. Thus, Hertz,[2] by means of barium and the roentgen ray, says the rate depends on the time of ingestion and defecation, and gives figures from nine to thirty-two hours. Then Case[3] believes that the colon should be empty by the end of thirty-six hours; but Barclay[4] says that there are plenty of women in

* From the Skin Clinic of the Massachusetts General Hospital.

1. Cannon, W. B.: The Mechanical Factors in Ingestion, New York, Longmans, Green & Co., 1911, p. 2.
2. Hertz, A. F.: Constipation and Allied Intestinal Disorders, London, Henry Froude, 1909, p. 12.
3. Case, J. T.: Roentgenologic Aspects of Intestinal Stasis, Med. Clin. Chicago **1**: 849, 1915-1916.
4. Barclay, A. E.: The Alimentary Tract, New York, the Macmillan Company, 1917, p. 119.

Digitized by Google

whom the opaque meal takes forty-eight hours or longer to reach the rectum. And Straus,[5] by the use of carmin, gives twelve hours as the minimum and forty-eight as the maximum for normal limits. Finally, I have suggested that the normal time is about sixty-four hours.[6] Such variations are readily explained in a large series of determinations; especially when it is found possible to change the rate in a subject by dietary treatment.

In this investigation of the intestinal rate, the estimates were made by the study of forty plates in roentgen-ray exposures taken five, ten, twelve, twenty-five and fifty hours after the ingestion of a barium meal; but more often by seeds given sixty subjects in 250 tests and observed in about 1,000 stool examinations. The tests counted were only those of subjects having one or more natural dejections daily. In one series of roentgen-ray exposures, only a little barium remained in the colon after twenty-five hours. Such a condition is associated with soft and formless feces. In another series however, not only was most of the barium apparent in the colon in fifty hours, but in the sigmoid it was formed into discrete masses. This condition is always associated with feces entirely composed of discrete masses or fecal units. The first series was taken of a patient with psoriasis, whereas the last series was of an unusually healthy individual.

While the roentgen ray method is applicable in a large hospital, it is too intricate and expensive for general use; accordingly another means was devised, which, though simpler, is sufficiently accurate to give very striking results. By this method a measure of 50 c.c. of French millet seed was given a subject immediately after an evening meal. Then the subsequent dejections were examined, and the time noted when more than five seeds were first and last seen. In this

5. Straus, H.: Arch. f. Verdauungs kr. **20**, 1914.
6. Burnett, F. L.: Fecal Units and Intestinal Rate, a Basis for the Study of Health and Intestinal Indigestion, Boston M. & S. J. **184**: 371 (April 14) 1921.

Digitized by Google

way the number of hours elapsing from the time of ingestion to the appearance of the seeds gives the initial rate; while from the time of ingestion to the hour when the seeds were last seen is the measure of the final rate. That is to say, if seeds taken on Monday at 6 p. m. were first seen on Tuesday at 8 a. m., the initial rate is fourteen hours; and then if they continued to be apparent until Thursday at 8 a. m., the final rate is sixty-two hours. With such a rapid rate the stool is always soft and formless. On the other hand, when the seeds pass through the intestine at a moderate speed, or with an initial rate of about twenty-five hours and a final rate of about ninety-seven hours, the dejection is indented by irregular lines across the mass, or is formed with marks. And finally, with a slow rate of sixty-two and 134 hours, the stool not only bears the lines, but is also entirely composed of discrete masses or fecal units.

These figures represent a uniform speed of the intestinal contents in their passage during the test; but very frequently the rate varies and becomes acclerated or retarded, and then there is a corresponding change in the form of the feces. When there is an acclerated rate, the specimens are always large and exhibit several features, as units, marks and formless portions and express a change in the initial rate from sixty-two to twenty-four or even fifteen hours. On the other hand, when the rate is retarded, the specimens are small, made up in a firmer mass, and may be composed of small and undersized units. Such forms may express a change in the initial rate from fifteen to twenty-five or thirty-nine hours.

The object of this study has been not only to correlate the intestinal rate with the form of the feces, but actually to retard the rate, in order to get patients with eczema and psoriasis on a unit basis, and in this way relieve intestinal indigestion.[7] The treatment consists

7. A paper on intestinal indigestion in eczema and psoriasis is being prepared.

Digitized by Google

in refining the alimentary mixture, and by this means the intestinal rate is retarded, as shown in Table 1. We have been led to believe that a slowing of the intestinal contents is always the cause of autointoxication and a great many secondary conditions of disease. This form of food poisoning undoubtedly does occur, but evidently in those with an unrefined mixture. From a study of a few of these patients, such a mixture generally evokes a rapid intestinal rate.

Some of the estimates actually obtained are as given in Table 1.

TABLE 1.—INTESTINAL RATE DETERMINATIONS

B. R. Date		Rate	*McL.* Date		Rate
22	X	15—39	18	VII	12—23
29		15—39	25		15—88
6	XI	16—63	1	VIII	24—X *
13		16—63	8		49—188
20		16—85	15		15—117
27		16—64	22		15—102
31	XII	18—85	29		15—X *
28	I	15—89	5	II	63—184
C. O. Date		Rate	*B. U.* Date		Rate
7	VII	25—96	8	I	63—135
12		24—48	15		63—115
3	X	64—X *	22		87—134
7	I	17—42	29		63—146
29		43—115	5	II	63—146
12	II	44—113	12		63—147
27	III	45—96	19		39—160
24	IV	64—139	26		63—160

* Not observed.

B. R. was a patient with constipation and eczema, who found on refining the alimentary mixture that his movements became more regular without laxatives, and the eczema improved. McL. had psoriasis, and improved on dietary treatment only. C. O. was another psoriatic, who, while on a unit basis and a slow intestinal rate, recovered entirely. At this time he felt unusually well, but got careless about his diet, changed his rate to 17-42, and with the accompanying change in the character of his stool had another attack. Finally he resumed treatment, once more got on a unit basis with a rate of 64-139, and

Digitized by Google

the lesions have almost disappeared. B. U. is an unusually healthy individual having a slow rate of about 63-147 for many years. Estimates of the intestinal rate are of practical value in keeping a check on patients having previously been subject to dietary errors, as shown in Table 2.

The significance of the semisolid form of the feces or diarrhea is sufficiently obvious to require comment. The soft and formless dejection with an irregular surface, in contrast to one formed with marks, or more particularly to one with marks and units too, must have some meaning. Such pronounced features in two of the types must be due to some of the functions of the intestine; and in order to compare these features

TABLE 2.—INTESTINAL RATES TO CHECK PROPER NOURISHMENT

Date	*S. W.*	Rate
1	XI	38—145
10	XII	39—148
11	II	50—110
6	III	49—145

with the actions, it is well to review the intestinal motility. In general there are three essential forms of motility: rhythmic segmentation in the small intestine, peristalsis and antiperistalsis in the proximal colon, and haustral churning or segmentation in the distal colon. The action of the small intestine need not be taken into consideration, as it probably does not influence the form of the feces. On the other hand, after the soft and pultaceous material has been kneaded back and forth in the proximal colon, it is formed into discrete masses by the action of a series of constructing rings in the intermediate colon. Then these small masses or units are evidently a sign that the ingested material has completed peristalsis and antiperistalsis in the proximal colon. In the distal colon the units travel slowly onward by the movement of Fischl and Porges, but are once more acted on by constrictions of the intes-

Digitized by Google

tine in haustral churning or segmentation. Case [8] says this process is similar to rhythmic segmentation; and so the marks or lines shown on the units and specimens formed with marks are evidently due to this function. Accordingly the significance of the forms of the feces without doubt is this: The unit form of the feces is an indication that the intestinal contents have completed the three essential forms of motility of the intestine; the one formed with marks is an indication of rhythmic and haustral segmentation. Such a contention is borne out not only by figures on the intestinal rate, but also by success in the treatment of cases. Specimens formed with marks will appear after a while if the patient follows directions; but the unit form of the feces requires long continued and exacting efforts to produce.

Is it possible to consider the significance of the feces further, and call one normal, and the others abnormal? The soft and formless dejection is a common type. On the other hand, the unit form of the feces is in the first place similar to the normal form of the higher animals. In the second place it conforms to the physiology of the intestine; and in the third place the requirements necessary to produce it are exacting, and when not fulfilled the stool changed to a soft and formless condition. And finally, individuals found regularly on a unit basis are unusually healthy, and those changed to this basis by treatment—without the aid of any other measures—have improved in health, and been relieved of very resistant forms of eczema and psoriasis. Therefore it is difficult not to say that the unit form of the feces is normal, and that the intestinal rate of about 60-140 hours always accompanying this form, is normal. In this way the form of the feces affords a very definite and immutable means of determining two heretofore unrecognized conditions of the body. One is intestinal indigestion as determined by the soft and formless stool. Such a condition is always associated with malnutrition,

8. Case, J. T.: M. Clin. Chicago **1**: 747.

Digitized by Google

and may be with an excessive or peculiar putrefaction of the intestinal contents; and these factors are likely to be the cause of some of the secondary conditions of disease. The other is an improved state of well being, as determined by the unit form of the feces. In this condition the individual evidently received the nourishment in amount and kind that should be obtained from the food. To be almost constantly receiving proper nourishment from the food is undoubtedly the crucial factor in preventing eczema and psoriasis, and it may be in preventing other secondary conditions of disease, as it must be the most important factor in the maintenance of a harmonious and healthy body.

205 Beacon Street.

Digitized by Google

DOES CANCER ARISE IN CHRONIC GASTRIC ULCER?*

WILLIAM CARPENTER MacCARTY, M.D.
ROCHESTER, MINN.

There are two questions which have been almost constantly asked by members of the medical profession: Does cancer arise in chronic gastric ulcer? and What percentage of chronic gastric ulcers become malignant? These are unquestionably interesting and important inquiries, but their practical clinical significance has been greatly overestimated; the rather vicious discussion which has taken place in medical societies and in the literature has probably done some harm. Many physicians do not differentiate the things which are of purely scientific interest from those which are of practical importance. From a purely scientific standpoint, neither one of the questions as stated can be correctly answered. No one should state positively that cancer arises in chronic gastric ulcer until one experimentally produces chronic gastric ulcer and produces cancer in the ulcer, and then shows that all of the conditions of the experiments are comparable to the conditions which arise in human beings.

In the literature on the subject, practical surgeons and practitioners of medicine have misinterpreted published scientific facts relative to the close association of gastric ulcer and cancer, and have thought that those working on the subject had clearly demonstrated the origin of cancer in ulcer. They have confused association with origin, and hence a certain amount of chaos has arisen which has unintentionally misled the medical profession and brought about a state of uncer-

* From the Mayo Clinic.

Digitized by Google

tainty in the minds of the lay public relative to professional opinion.

If one were able to state the exact percentage of ulcers associated with cancer, or cancer associated with ulcer, from one year's experience, it would be seen to vary from year to year.

The important practical question is: Is cancer often associated with chronic gastric ulcer? From an experience of more than 1,400 gastric specimens, I can state that the association is so frequent that if I had a chronic gastric ulcer I should always consider the possibility of cancer being present, and I know of no clinical or laboratory methods by which the differential clinical diagnosis can be made. From actual experience also I know that most chronic gastric ulcerations with a diameter greater than 2.5 cm. are cancerous. I do not know whether the cancer or the ulcer was primary, but I do know that I would not temporize with the chronic gastric ulcer.

Ulcers of the stomach may be divided, for practical purposes, into five groups:

1. The simple acute peptic ulcer.
2. The chronic ulcers which are tuberculous or syphilitic.
3. The chronic ulcer, the exact etiologic factors for which are unknown.
4. The chronic ulcer in which there is a neoplastic process in the borders of the mucosa.
5. The gastric ulcer which shows carcinoma not only in the borders but also in the base.

There are no positive clinical signs, symptoms or laboratory tests by which these five groups of ulcers can always be differentiated, but it is very rare in my experience to see an acute peptic ulcer, a tuberculous ulcer or a syphilitic ulcer resected by my colleagues in surgery.

The last three groups of ulcers cannot always be differentiated clinically, or even grossly, after the ulcer has been resected. In my studies of 733 chronic

Digitized by Google

gastric ulcerations, the differentiation was made in 29 per cent. only with a microscope.

Advanced carcinomas may be seen with the roentgen ray, and if the roentgenologist discovers an ulcer which he estimates to be larger than 2.5 cm. in diameter, the guess of cancer will be correct in a very high percentage of cases. It is, however, only a guess for practical purposes, but has some value.

Ulcers vary in shape and size; they may be multiple or single; one of the multiple ulcers may be simple and the others carcinomatous; they are usually confined to the pyloric end of the stomach, and are usually near the lesser curvature or posterior wall.

If one examines a large series of specimens, he will find three groups of cytologic findings in the gastric tubular glands:

1. The glands of the borders are sometimes composed of cells which have the morphology of normal gastric gland cells. The picture is certainly not that of cancer.

2. The glands of the borders of some ulcers (grossly indistinguishable from those of the first group) show the fact that the columnar cells of the normal gastric tubules are replaced by ovoid or spheroid cells which are morphologically indistinguishable from cancer cells. Such cells are intraglandular. I do not know that this is cancer, but the cytologic findings arouse suspicions that it might be a precancerous condition.

3. The glands of the borders of certain chronic gastric ulcers (grossly indistinguishable from those of the first and second groups) are identical with those of the second group plus the presence of the ovoid or spheroid cells in the stroma of the mucosa, or in the other gastric coats and sometimes in the base of the ulcer.

How to distinguish these three groups clinically I do not know, but I do know that, with our present methods, surgery and a microscopic examination offer the only means of making the differentiation in a large

Digitized by Google

percentage of cases. Whether or not the members of the profession agree on the therapy to be applied to chronic gastric ulcer, it is certain that surgery offers the only means, with our present knowledge, of making the correct diagnosis, and certainly we have no medical or dietetic method of treating cancer.

CONCLUSION

It is important to make the diagnosis, and the differentiation of simple chronic gastric ulcer and early carcinomatous gastric ulcer cannot be made clinically. The important fact to be fully appreciated by the members of the medical profession and by the laity is the common association of gastric ulcer and cancer and the present impossibility of always making a clinical differentiation.

ABSTRACTS OF DISCUSSION

Dr. Herbert R. Brown, Rochester, N. Y.: I should like to ask Dr. MacCarthy whether he has ever seen carcinoma develop as a primary entity without preliminary inflammatory process? It is my impression that some European pathologist is of that feeling, but as I look over tissues I have examined I cannot recall such a case. In regard to carcinoma, it seems logical that it should develop from the periphery owing to changes in hydrogen ion composition.

Dr. John J. Gilbride, Philadelphia: Surgeons now know that the best treatment for gastric ulcer is the excision of the ulcer. As Dr. MacCarthy says, it is difficult to make a diagnosis of a specimen when it is out and on the table. It can easily be seen how much more difficult it is to make a diagnosis of the condition while it is in the abdomen. From the histories of cases of cancer of the stomach, experience has taught that there are practically two groups if one wishes to group them arbitrarily. In one group of patients the history extends over a long period of time. This is suggestive that these patients have suffered from some form of chronic irritation, which might be the beginning of malignancy. In the other group, the onset appears to be comparatively sudden. Of course, we may have hardly any early symptoms in carcinoma of the stomach as long as there is no obstruction.

Dr. J. Shelton Horsley, Richmond, Va.: Many persons have been hanged on circumstantial evidence which is not so strong as that presented by Dr. MacCarty for the incidence of carcinoma with gastric ulcer. I should like to ask Dr. MacCarty whether he finds the same histologic appearance

Digitized by Google

with duodenal ulcer as he has shown with gastric ulcer. It seems hardly probable that in such early histologic changes as Dr. MacCarty has indicated there be any clinical symptoms of significance.

DR. PHILIP HILLKOWITZ, Denver: The question of incidence of irritation and origin of neoplasms has been taken up by pathologists just as it has by clinicians. I am glad to hear Dr. MacCarty make the statement that he does not know. We have overemphasized the causative fact of overirritation. Much radical surgery has been done, and, in my opinion, unnecessarily. A great deal of emphasis has been laid on the so-called precancerous stage, which in my opinion does not exist. I remember the time when we spoke of the pretuberculous stage. When we did not know the cause of tuberculosis we said it was due to cold. How rarely do we find carcinoma of the hand? The consequences of this and other far fetched teachings is that breasts have been removed unnecessarily, and cervices have been taken off on account of laceration. Carcinoma will develop even at the site of an amputed cervix. The conclusion that Dr. MacCarty reaches is, "If I have an ulcer of the stomach I want it taken out." You must remember that the practitioner in every community looks to what is done here. We must remember our responsibility. It is not a very simple operation, and we should feel our way carefully as to our responsibility for our words. It is all right to discuss from the academic standpoint as to whether irritation is the cause of cancer, but in the application, the question is a weighty one and involves a great deal of responsibility.

DR. WILLIAM H. STEWART, New York: Some unfortunate experience must be accountable for Dr. MacCarty's constant reference to the inability of the roentgenologist to differentiate between malignant and benign lesions of the stomach. Most conservative roentgenologists agree with the author that small, budding, penetrating ulcers are benign—at least, the roentgenologist, as well as the surgeon and the pathologist, is not able to differentiate between these benign ulcers and those which are malignant. The microscopic examination is the one any only accurate method. When these penetrating ulcers assume an unusual size, such as a diameter of 2 cm., they are usually malignant. Early annular growths of the pylorus can be recognized roentgenographically. They are especially malignant. Growths producing irregular defects in the stomach outline are easily recognized as cancer.

DR. D. J. DAVIS, Chicago: Dr. MacCarty has called attention to the fact that if these ulcers are approximately 2.5 cm. in diameter, the probabilities are that they are malignant. I wonder whether his data will permit of an analysis in actual percentage.

DR. EUGENE L. OPIE, St. Louis: My experience is in accord with the view of Dr. MacCarty that it is seldom, if ever,

Digitized by Google

possible to obtain evidence that cancer has developed on an ulcer. He has emphasized the similarity between the ulceration of cancer and peptic ulcer. It seems to me not unlikely that the conditions that bring about the ulceration of cancer are very similar to those that bring about peptic ulcer. One of the essential features of peptic ulcer is its failure to heal, and with a considerable variety of injuries to the stomach peptic ulcer may occur. The gastric juice doubtless has an important part in dissolving injured tissue. With the injury caused by cancer, superficial ulceration is likely to occur. Ulceration and subseqent solution of tissue may destroy all the cancer in the center of the growth, but cancerous tissue still remains in the edges of the ulcer. These changes may explain some of the histologic characters which have been cited as evidence of the development of cancer on a peptic ulcer.

Dr. W. C. MacCarty, Rochester, Minn.: The question of cancer developing without injury is a big question. I give you my personal opinion. I have studied the histogenesis of neoplasms, and I do not believe that any neoplasm occurs without a previous injury, not necessarily something which we can see grossly. I am speaking of chemical injury. As to the clinical history, the most extensive cancer of the stomach I ever saw gave a clinical history that could not be interpreted as cancer until a week before the patient died, and then he had obstruction of the common duct and jaundice, and we knew what he had. So the history is not always an index as to whether there is cancer. In duodenal ulcer, we did not see these cytologic changes. I do not like the word "precancerous," I rather prefer "pro," using it in the same sense as "pro" botany. Precancerous means to me everything that goes before development of cancer. I have never seen a cancer of the breast in which I could not show definitely that there was not an inflammatory condition present at the time. I wish to apologize to Dr. Stewart; I have no reflection to make on radiologists, and the best paper I have read on this subject was read before the Radiological Society. I have always hoped in dealing with the radiologists to get rid of the extremists who say they can always diagnose gallstones. Dr. Davis spoke of size and percentage of malignancy I have not compiled any statistics. I am frequently quoted in this country and abroad as giving a percentage. I have never yet given a percentage of gastric carcinoma. Dr. Opie asked about ulceration. The same histologic pictures are seen in cancer of the stomach as we see in simple ulcer of the stomach. The reaction is all the same. I do not know how we are going to settle this question whether these are ulcerated cancers or cancerous ulcers.

Digitized by Google

ACUTE DILATATION OF THE STOMACH *

LESTER R. DRAGSTEDT, PH.D., M.D.
AND
CARL A. DRAGSTEDT, M.S., M.D.
CHICAGO

The etiology and pathogenesis of acute dilatation of the stomach and its attendant phenomena are for the most part obscure. A considerable number of exhaustive clinical and pathologic studies of this interesting and important phase of gastric pathology have appeared in recent years, notably those of Conner,[1] Borchgrevink[2] and Novak.[3] A careful scrutiny of reported cases seems to have definitely established a number of significant points. Following the example of Conner, it has been customary to classify the cases on the basis of a chief pathologic factor common to certain groups, and it was found that many followed operations under general anesthesia, which was usually chloroform. Others developed during the course of, or convalescence from, severe and wasting diseases, after injuries, after errors in diet associated with sudden overloading of the stomach, and in persons with spinal deformities of various kinds. To these groups probably should be added those cases of acute postpartum dilatation of the stomach which are reported with increasing frequency in obstetric literature. As emphasized by Doolin,[4] if the pathologist has this condition in mind, at the

* From the Hull Physiological Laboratories of the University of Chicago and the Department of Surgery of Rush Medical College.

1. Conner, L. A.: Acute Dilatation of Stomach and Its Relation to Mesenteric Obstruction of the Duodenum, Am. J. M. Sc. **133**: 245, 1907.
2. Borchgrevink, O. J.: Acute Dilatation of the Stomach and Its Treatment, Surg., Gynec. & Obst. **16**: 662, 1913.
3. Novak, Emil: Acute Postoperative Dilatation of the Stomach, J. A. M. A. **77**: 81 (July 9) 1921.
4. Doolin, W.: Acute Dilatation of the Stomach, Brit. J. Surg. **6**: 125 (July) 1918.

Digitized by Google

necropsy a dilated stomach and a duodenum partly or completely obstructed are the chief anatomic findings. The unsettled questions are the relations which these conditions bear to one another, their etiology and pathogenesis, and their relation to the other phenomena of the disease, namely, the enormous accumulation of secretions in the stomach, the dehydration, the collapse, and death.

ETIOLOGY AND MECHANISM OF ACUTE DILATATION OF THE STOMACH

The occurrence of acute gastric dilatation during the course of an abdominal operation indicates that the mechanism is probably a nervous reflex. The recent experiments of Carlson and Luckhardt[5] demonstrate that it is possible to obtain both somatic and visceral reflexes from the stimulation of either somatic or visceral sensory nerves. Relaxation of the stomach has been observed following direct stimulation of the peripheral splanchnic nerves or reflexly through stimulation of many of the abdominal viscera. Although the operation has been performed a great number of times in the study of various problems, a section of both vagus nerves above the diaphragm, or a combined section of both vagus nerves and splanchnic nerves in dogs has never in our experience produced a dilated stomach with adverse symptoms. The work of Carlson, Luckhardt, Alvarez and others indicates that the alimentary tract possesses a peripheral automatic mechanism similar to that of the heart or amphibian lung, and a section of its extrinsic nerves does not produce gastric paralysis any more than section of the vagus or sympathetic branches to the heart results in paralysis of the cardiac musculature. There is direct experimental evidence as well as clinical observation that ether or chloroform anesthesia depresses the gastric tonus, and this no doubt may be a contributory

5. Carlson, A. J., and Luckhardt, A. B.: Vagus Control of the Esophagus, Am. J. Physiol. 57: 299 (Sept.) 1921.

Digitized by Google

factor in many cases. It is not probable that the absorption of toxic materials from the occluded upper intestinal tract or duodenum plays an important rôle in the gastric dilatation, since this was never observed in animals in which a toxemia similar to that of high obstruction was induced by the production of closed intestinal loops.[6] In these experiments the effect of the poisons could be observed independently and free from any mechanical distention produced by retained contents. When injected intravenously, these toxic materials produced marked motor activity of the entire gastro-intestinal tract; but a depression or paralysis was never observed. It can be easily demonstrated experimentally that a stenosis of the duodenum will result in a gradual dilatation and hypertrophy of the part above the obstruction and the stomach. An acute dilatation of the stomach is rarely, if ever, produced by such a stenosis.

RELATION OF DILATED STOMACH AND OBSTRUCTED DUODENUM TO COLLAPSE AND DEATH

It is quite improbable that the dilatation of the stomach is responsible directly for the protean symptoms that accompany the condition. When such an acute dilatation has occurred on the operating table and been relieved by the introduction of a stomach tube, the immediate reflex disturbances are slight and are not characteristic. A distention of the stomach of a dog under ether anesthesia, after ligation of the cardia and pylorus, gave rise to temporary reflex effects on distant organs; but the condition of the animal was not bad, and complete recovery took place when the ligatures were loosened and the air released. A distention of the stomach of both anesthetized and unanesthetized dogs with rubber balloons never produced acute dilatation,

6. Dragstedt, L. R.; Moorhead, J. J., and Burcky, F. W.: Intestinal Obstruction, J. Exper. Med. **25**: 421 (March) 1917. Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. S.: Ibid. **30**: 109 (Aug.) 1919.

Digitized by Google

although the pressure was raised sufficiently to cause vomiting movements.

The symptoms, such as vomiting, thirst, scanty urine, and rapid collapse, which often make it difficult to distinguish the condition from perforative peritonitis or intestinal obstruction, are those of a severe toxemia rather than the result of reflex or mechanical effects from the stretched and dilated stomach. The view of Rokitansky, Albrecht, Conner and others places the essential pathologic condition not in the stomach but in the obstruction to the third portion of the duodenum. The mechanism of this obstruction by the mesentery and some experimental data illustrating factors which may bring it about are given by various writers.[7] The explanation given by Borchgrevink that there occurs a primary gastric dilatation and secondary mechanical occlusion of the duodenum, either by the direct pressure of the stomach on the duodenum in its passage over the spine or by a secondary arteriomesenteric compression brought about by the downward pressure of the dilated stomach which forces the small intestine into the pelvis, is supported by these experiments. There is no conclusive evidence that an arteriomesenteric occlusion of the duodenum as a result of a long and dependent mesentery can ever cause a dilatation of the stomach, although, as will be seen; it may cause a severe toxemia.

During the course of an experimental study of acute intestinal obstruction, certain facts were forced to our attention which have great significance for the present problem. In those experiments it was demonstrated that the toxic materials, which in the event of an acute high obstruction entered the blood stream and caused a sudden and fatal toxemia, had their origin in the intestinal tract as a result of the activity of proteolytic intestinal bacteria. Of even more importance, however, than the presence of these toxic bodies in the

7. Albrecht, P. O.: Ueber arteriomesenterialen Darmverschluss an der Duodenojejunalgrenze und seine ursachliche Beziehung zur Magenerweiterung, Virchows Arch. f. Path. Anat. **156**: 285, 1899. Rokitansky: Lehrbuch der pathologischen Anatomie **3**, 1863.

Digitized by Google

intestine are the factors which permit their absorption. They are not absorbed through a normal intestinal mucosa, but are absorbed when the blood supply to the intestinal wall has been disturbed by great distention. Organs, such as the colon or stomach, which have in part a storage function are capable of very great distention without injury by reason of the arrangement of their blood supply. On the other hand, the small intestine, especially the duodenum, is capable of practically no dilatation. By reason of its investment in a tough, fibrous envelop and the position of its nutrient vessels, which are arranged parallel to its long axis, any distention of the duodenum must result in an immediate circulatory damage. Irrespective of whether the mesenteric obstruction of the duodenum be due to a downward drag of the small intestines in the pelvis or be secondary to a dilatation of the stomach which forces the intestines down, it is obvious that the obstruction to the duodenum cannot be very great. This is confirmed by postmortem observations, in which it is usually found that the obstruction can be easily overcome by the examiner's finger, a fact which has led many to question the importance of the duodenal obstruction in the pathogenesis.

In a study of some of the functions of the duodenum,[8] it was necessary to produce duodenal fistulas of various kinds for the collection of secretions. The pylorus was closed, a gastrojejunostomy performed, and the lower end of the isolated duodenum brought to the surface through the rectus abdominis muscle. Although a similar type of fistula in the jejunum, ileum or colon was found to be without harm, most of the animals with duodenal fistulas died very promptly, often within forty-eight hours. The symptoms were those of a severe toxemia, with vomiting and rapid collapse. Similar observations had been made

8. Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. S.: Extirpation of the Duodenum, Am. J. Physiol. **46**: 584 (Aug.) 1918.

Digitized by Google

before by Matthews and Pilcher,[9] and by Whipple.[10] At the necropsy, the isolated duodenum was usually slightly distended, but otherwise normal. Apparently the abdominal muscles had acted as a sphincter and prevented the free escape of the duodenal secretions. In later experiments, care was taken to prevent this type of obstruction by placing a rubber catheter in the duodenum and washing it daily. When this was done, no adverse symptoms appeared, and animals could survive for long periods with such duodenal fistulas.

These observations, which demonstrated that a slight obstruction, of a degree which would have no effect in the small intestine or colon, would in the duodenum result fatally, suggested the following type of experiment: Obstructions of varying degrees were produced in the lower duodenum by means of light rubber bands. In two experiments, an ordinary rubber band about 1.5 cm. wide was placed around the duodenum, drawn barely tight enough to collapse the intestine and close its lumen, and stitched in place. In three experiments a still slighter obstruction was secured by using a band made of thin condom rubber, 2 cm. wide, again drawn just tight enough to collapse the intestine. Four of the animals died promptly within seventy-two hours with the usual symptoms of acute high obstruction. At the necropsy, the duodenum above the occluded area in each case was slightly distended, but the stomach was firmly contracted, especially in the pyloric region. In each case the degree of obstruction caused by the rubber band was very slight, and could be easily forced by the examiner's finger. In two cases the obstruction was forced by a column of water 6 inches high. An obstruction of this degree does not produce any symptoms whatever if it is produced in the lower jejunum, ileum or colon.

9. Matthews, A. P.: Physiological Chemistry, New York, 1915, p. 388.
10. Whipple, G. H.: J. Exper. Med. **15**: 259, 1912. Whipple, G. H.; Stone, H. B., and Bernheim, B. M.: Ibid. **17**: 286, 307, 1913; **19**: 144, 166, 1914.

Digitized by Google

The facts developed from animal experimentation indicate that a severe or fatal toxemia could quite easily arise in man from an arteriomesenteric obstruction to the duodenum; but when this is a primary factor there is no evidence to indicate that dilatation of the stomach would probably follow. Such an occlusion has never produced an acute dilatation in the dog. It is probable that the dilatation is the primary factor, but that the toxic symptoms are dependent on the secondary duodenal occlusion. It is not unreasonable to suppose that the clinical symptoms of uncomplicated duodenal stenosis and duodenal stenosis plus a dilatation of the stomach should be somewhat different, although the origin of the toxemia is the same in the two cases. It is not probable that the source of the toxemia is absorption from the dilated stamach. In all of our experiments it was noted that toxemia usually occurs within a few hours after distention of a closed loop and interference with its blood supply. In gastrectasis following surgical operations, however, the toxic symptoms are usually delayed two or three days until a time when the duodenal occlusion could have developed, and a distention could have taken place. It is difficult to see how a dilatation of the stomach of reflex origin could take place two or three days after the inciting trauma of the operation. It is more probable that the dilatation is immediate but unrecognized until the secondary duodenal occlusion has produced the toxic symptoms.

ORIGIN AND NATURE OF VOMITED FLUID

One of the most striking features of the disease is the enormous quantity of fluid which is regurgitated or may be aspirated from the dilated stomach. This is far in excess of the fluid intake, and the excessive thirst and scanty urine testify to the dehydration produced. Many observers have noted the rapid filling of the stomach after it has been completely emptied by a stomach tube. In most cases in which examination

Digitized by Google

was made, the fluid contained little or no free hydrochloric acid, and practically always contained bile, as shown in the accompanying table. A study of these cases suggests that the fluid is made up of not only gastric juice but also bile, pancreatic juice, and perhaps the duodenal secretion as well. It is quite evident that the great amount of fluid present cannot be the normal output of the glands in question, but must represent the result of a profound stimulation. The mechanism of this secretion has not been adequately studied. Although a part of the normal gastric secretion is dependent on reflex stimulation of secretory fibers in

TABLE 1.—ANALYSIS OF GASTRIC CONTENT IN CASES OF ACUTE POSTOPERATIVE DILATATION OF STOMACH *

				Gastric Contents			
				Free	Total		
No.	Operation	Anesthetic	Onset	HCl	HCl	Bile	Blood
1	Inguinal hernia.....	Gas-ether	48 hrs.	+	+	+	+
2	Kidney stone.....	Ether	36 hrs.	No examination			
3	Mesenteric fibroma.....	Gas-ether	48 hrs.	0	0	+	0
4	Prostatectomy.....	Ether	48 hrs.	0	0	+	0
5	Cholecystectomy.....	Ether	24 hrs.	0	0	+	0
6	Resection of stomach.....	Ether	120 hrs.	0	0	+	0
7	Appendectomy.....	Ether	48 hrs.	0	0	+	0
8	Gastro-enterostomy.....	Ether	36 hrs.	0	0	+	+

* From records of the Presbyterian Hospital of Chicago.

the vagus nerves, it is not probable that nervous influences play any significant part in the production of this fluid. Most of the evidence indicates a depression rather than an increased vagus tonus. The previous studies, which suggest so strongly the simultaneous presence of a duodenal occlusion of a degree sufficient to cause a severe toxemia or death, if unrelieved, afford a clue to the nature of the stimulus. It is known that the toxemia of acute high intestinal obstruction is accompanied by the secretion of great quantities of fluids into the stomach and intestine above the obstructed area. A study of the physiologic activity of the poisons of acute obstruction has demonstrated that these are very active secretagogues, and it is quite

Digitized by Google

probable that some of them are identical with the so-called secretion bodies which may be obtained from the duodenal mucosa and which have such a striking effect on the secretion of gastric and pancreatic juice. Animals were prepared for the experiments in the manner suggested by Luckhardt, Palmer and Henn,[11] which permits of the simultaneous collection of the secretions of the stomach, the bile, the pancreatic juice and the duodenal secretion from animals in comparatively good physiologic condition. Sublethal doses of fluid obtained from an obstructed duodenum or closed intestinal loop, when injected intravenously into such animals, were

TABLE 2.—EFFECT OF INTRAVENOUS INJECTION OF TOXIC SUBSTANCES OBTAINED FROM THE DUODENUM ON THE SECRETION OF DIGESTIVE JUICES IN THE DOG

	Gastric Secretion					
Procedure	Volume, C.c.	Free Acid	Total Acid, Units	Duodenal Juice, Drops	Pancreatic Juice, Drops	Bile, Drops
Normal rate of secretion 30 min..	3	0	4	53	52	22
Normal rate of secretion 30 min..	3	0	4	59	56	30
Intravenous injection of toxic substances from duodenum:						
1st 30 min. period.....	3	0	8	100	70	40
2d 30 min. period.....	3	0	8	135	50	58
3d 30 min. period.....	5	0	7	75	21	39
4th 30 min. period.....	5	0	7	82	20	25

found to produce a striking increase in all of the secretions. The fluid expelled from the stomach in acute high obstruction or acute dilatation of the stomach is doubtless made up of the greatly augmented products of all of these glands and the stimuli to its production are chemical rather than nervous reflexes. It should be noted that in both of these conditions the excessive secretion may result in considerable dehydration. The dehydration is, however, produced by the entrance of these toxic substances with their secretagogue action into the blood stream, and cannot be considered a primary factor in any sense.

11. Luckhardt, A. B.; Palmer, W. L., and Henn, S. C.: On the Specificity of Gastrin and Pancreatic Secretin, Am. J. Physiol., to be published.

Digitized by Google

RELATION OF ACUTE DILATATION OF STOMACH TO TETANY

Tetany is a symptom not uncommonly associated with gastro-intestinal disturbances, and is notably frequent in acute dilatation of the stomach. Heretofore the common explanation has ascribed these manifestations as of reflex origin from the irritated intestine or the distended stomach. In a series of experiments reported elsewhere,[12] we have demonstrated that the tetany which appears in animals following removal of the parathyroid glands is dependent on the absorption of toxic substances from the intestinal tract. These substances, in common with those which are responsible for the toxic symptoms in acute dilatation of the stomach, are produced in the lumen of the intestinal tract by the activity of the proteolytic group of intestinal bacteria. They are not true bacterial toxins, but represent various toxic protein fractions arising from the partial splitting of the protein molecule by the bacterial enzymes. A practically complete removal of the proteolytic bacteria from the intestine or a change in their metabolic processes may be secured in animals by feeding a carbohydrate diet which contains definite amounts of either lactose or dextrin. There is definite experimental evidence that these changes in the intestinal flora reduce the toxicity of the intestinal content.[13] When the parathyroid glands are removed from such animals, tetany does not appear, and the animals may survive indefinitely. A natural inference is that the parathyroid glands in some way exert a detoxifying function particularly concerned with these intestinal poisons, which apparently find their way into the systemic blood stream in appreciable quantities. A parathyroid deficiency or complete absence would permit their accumulation in the body in sufficient concentration to produce the tetany. In acute dilatation of the stomach, it is probable that the tetany is due to the excessive absorption of these intestinal poisons beyond

12. Dragstedt, L. R.: Pathogenesis of Parathyroid Tetany, read before the Society for the Study of Internal Secretions, St. Louis, May, 1922.

Digitized by Google

the ability of the parathyroids to care for them, or there may have been a preexisting parathyroid deficiency so that its factor of safety was easily overcome.

MECHANISM OF CURE BY POSTURAL TREATMENT AND GASTRIC LAVAGE

It has been definitely established that the excessive mortality formerly associated with acute gastric dilatation may be greatly reduced by the prompt use of the stomach tube and the adoption of the postural treatment advocated by Schnitzler. These cases are apparently so striking that any accurate explanation of the pathogenesis of the disease must afford a rational explanation of the beneficial results from such treatment. The frequent use of the stomach tube removes from the stomach and distended duodenum the toxic materials whose absorption is responsible for the toxemia, and also lessens the occlusion to the duodenum produced by the weight of the stomach. The adoption of the knee chest position or the prone position with elevation of the pelvis affords relief, and the explanation is undoubtedly that given by those who first advocated it; namely, it releases the mesenteric occlusion of the duodenum by removing the downward traction of the mesentery and the weight of the dilated stomach. We should expect that it would be more efficacious than the gastric lavage, since experimentally it was found that the factors which permit of the absorption of intestinal poisons, i. e., obstruction with distention, are far more important than the production of these poisons. This type of toxemia in dogs can be successfully controlled by the frequent administration of large amounts of Ringer's solution or salt solution intravenously or by hypodermoclysis. There is no reason why such treatment may not be tried in clinical cases.

ABSTRACT OF DISCUSSION

Dr. James J. Moorhead, Terre Haute, Ind.: Speaking of acute dilatation of the stomach from the clinical standpoint, I recently had this rather unusual experience: A patient was admitted to the hospital suffering from a gunshot wound

Digitized by Google

of the lower abdomen received thirteen hours previously. An enormous distention of the stomach was relieved by the use of a tube, and the patient was prepared for laparotomy. During the intra-abdominal work—six perforations of the small intestine were closed—a recurrence of the gastric dilatation subsided following the treatment employed in the first instance. Dr. Dragstedt's paper emphasizes the value of animal experimentation in the solution of clinical problems.

Dr. John J. Gilbride, Philadelphia: I was interested to hear from the pathologist as to his views on the etiology of acute dilatation of the stomach. My acquaintance with the subject was made in 1901 when I came across a little booklet of lectures on "Tumors of the Stomach," by the late Sir William Osler, which he delivered at Johns Hopkins Hospital. There is shown a plate of a necropsy in which the abdomen is opened and in which an acutely dilated stomach practically fills the entire abdomen. Acute dilatation of the stomach occurs most frequently after operations on the upper abdomen. However, it may occur after operation on any part of the body. It has occurred after operation on the head, and it has also occurred after the application of a cast or other apparatus for a support in disease of the spine. Both the motor and secretory functions of the stomach are profoundly affected. The stomach becomes hugely and rapidly dilated. There appears to be a profuse secretion into the stomach. This comes mostly from the stomach, and it is probably augmented by secretions from the pancreas and the liver. It appears to me that obstruction as an etiologic factor does not explain the condition. Personally, I believe that the statements made about compression of the duodenum by the superior mesenteric vessels are more mythologic than real. Gastro-enterostomy does not accomplish anything in these cases. Paterson had acute dilatation of the stomach occurring in two cases in which he had performed gastro-enterostomy for ulcer.

Dr. A. J. Carlson, Chicago: This work seems to link several known facts, particularly in connection with intestinal obstruction and intestinal intoxication, so that the interpretation offered must be refuted by something more substantial than mere guess. The work suggests a more rational therapy of that condition than gastro-enterostomy, because gastro-enterostomy would not necessarily relieve an obstructed duodenum. Dr. McKenna suggested some years ago the production of a fistula in the duodenum for the relief of general peritonitis, on the theory that some of the symptoms of general peritonitis involve interference with the duodenal functioning (obstruction). Would it not be feasible to introduce a duodenal tube for drainage of the obstructed duo-

Digitized by Google

denum via the mouth? This should be superior to the duodenal fistula operation for an obstructed duodenum, as this operation at times induces a more severe obstruction than the one we attempt to relieve by it.

DR. LESTER R. DRAGSTEDT, Chicago: We have never produced acute dilatation of the stomach in an experimental animal. A toxemia of high intestinal origin will cause death with practically all of the symptoms of acute dilatation of the stomach. There is no experimental evidence that dilatation or distention of the stomach will reflexly produce the symptoms we see in this condition. The beneficial effects of the adoption of the prone position with elevation of the pelvis and the use of the stomach tube can really be explained on the basis of the pathogenesis of the disease presented. The dehydration must be regarded as a result of the profuse secretion into the upper intestine and stomach, brought about by the toxic secretagogues and cannot be considered a primary factor. It would be relieved by the intravenous or hypodermic administration of Ringer's solution, which in addition would dilute and promote the excretion of toxic materials in the blood.

Digitized by Google

PULMONARY ASPIRATION OF PARTICULATE MATTER, NORMALLY AND DURING ANESTHESIA *

H. J. CORPER, M.D.
DENVER

There are many phases of medicine which are concerned with the question of the fate of particulate matter inhaled and aspirated into the lungs, especially when its distribution and mode of inhalation or aspiration is considered. From the standpoint of infection in pulmonary tuberculosis by the aerogenic route, it is usual to consider two main modes: the inhalation of dry pulverized sputum, as maintained by Cornet, and the inhalation of fluid droplets freshly expelled from the mouths of phthisical patients, believed by Flügge [1] to be the more probable. There is still another important mode, especially preferred by the adherents of the idea that childhood infection is paramount, and supported by the conception of the latency of the tubercle bacillus; that of the hand to mouth infection, occurring during the floor days of the child, as suggested by Krause.[2]

The problem is a complicated one, and in all probability at times any of these may be the mode of conveying the tubercle bacillus to virgin or susceptible soil, although it is impossible at present definitely to state without hesitation just how most pulmonary infections occur. It is rather singular that, in view of the droplet and hand to mouth suggestions, so little consideration

* From the Research Department, National Jewish Hospital for Consumptives.

1. Flügge, C.: Ztschr. f. Tuberk. u. Heilstättenw. **34**: 212 (May) 1921.

2. Krause, A. K.: New York State J. M. **21**: 83 (March) 1921; Am. Rev. Tuberc. **5**: 994, 1922.

Digitized by Google

has been given the pulmonary aspiration of fluids. Just as there is a difference of opinion regarding pulmonary infection in tuberculosis so the laryngologists do not all agree as to the mode of infection, during anesthesia, in lung abscess following operations on the upper respiratory tract, the three most prevalent conceptions being: aspiration from the upper air passages, lodgement from the blood stream and infection by lymphatic extention. That the aspiration of foreign bodies under certain circumstances occurs quite readily is universally accepted as a fact.

INTRAPULMONARY THERAPY

Viewing this subject from another angle, the feasibility of intrapulmonary therapy suggests itself. Can solids inhaled in very fine suspension, or liquids be introduced into the lung by the respiratory or aerogenic route, for application to diseased pulmonary sites? The distribution and fate of inhaled solids—soot, smoke or dusts has been carefully studied, on account of its enormous industrial and economic significance. In an elaborate American article by Klotz [3] on pulmonary anthracosis, replete with literature, some important points on the inhalation of carbon pigment (smoke) are emphasized. The deposition in the lungs of carbon pigment from the dust laden air is dependent on the respiratory function and the activity of the lymphatics. The inhaled air with its carbon particles is carried to varying depths in the lung tissue. The major amount of the foreign material adheres to the moist walls of the respiratory passages and never reaches the lung tissue proper. It is possible that the foreign material that adheres to the mucous membranes of the nose, pharynx, trachea and larger bronchi is but rarely carried into the tissues of these tracts, but, lying in the secreted mucus, is carried upward and is eventually expelled.

3. Klotz, Oscar: Am. J. Pub. Health 4: 887, 1914.

Digitized by Google

The relatively lesser quantity of dust and carbon which reaches the lung alveoli also becomes adherent to the moist surfaces of the alveolar sacs, and then, by the activity of certain cells, is eventually carried into the lymphatics of the alveolar wall, where they are disposed of by the lymphatic system of the part. The subsequent distribution is to a great extent determined by the site of absorption within the lung. The tendency of the absorbed carbon is to pass from the finer lymphatic channels of the alveolar walls to the larger passages, eventually reaching a lymph node, where the onward progress of the particles is impeded by the filtering action of this structure. In the main, the lymphatic drainage of the entire lung converges at the hilus and passes into the peribronchial glands located in this part.

Anthracosis in young adults is more prominent in the apex of the upper lobe, the anterior border of the upper lobe and the posterior border of the upper and lower lobes, but in these areas the distribution is by no means uniform. The unequal distribution of the pigment upon the pleural surfaces has no direct relation to the deposition within the lung. The lack of pigment on the interlobar surfaces and in the rib grooves is only a superficial condition and does not affect the deeper underlying lobules. The earliest deposits are mainly in the perivascular lymphatics of the smaller branches of the pulmonary artery; subsequently pigment appears in the regions of the smaller bronchi and venules.

In all of these situations, its presence becomes more marked with the increasing quantities of soot that are constantly inhaled. No evidence of excessive deposit in the deep tissues at the apex of the upper lobe was noted. More pigment was found toward the hilus than at the periphery, regardless of the pleural distribution.

In acute pneumonia, the involved areas show lesser pigmentation, with a sharp line of demarcation from

Digitized by Google

the more healthy tissues. In caseous pneumonia, there is only a moderate amount of pigment deposit in the caseous areas. In localized chronic caseous tuberculous foci, the pigment deposit increases in direct proportion to the amount of fibrosis. The fibrosed mass may become intensely black. It is probable that only those carbon particles lying within the alveolar sacs can reach a permanent interstitial abode, and that little if any carbon is phagocyted and carried into the tissues from the bronchi or bronchioles. Furthermore, it appears that the carbon reaching the lung alveoli is only a very small portion of the carbon content of the air as inspired, and this portion has reached the lung because it escaped contact with the moist mucous surfaces of the respiratory tract. Carbon deposits, by inducing fibrosis, tend to encapsulate chronic tuberculous foci.

Haythorn,[4] in reporting on the histologic evidences of the disease importance of pulmonary anthracosis, says:

> The fine particles seem to gain entrance into the lung substance by way of the air passages, and it has been stated by some that the mucous membranes of the nose, mouth, pharynx, and larynx, trachea, bronchi and bronchioles contribute largely to the taking in of the pigment, but our observations tend to show that, in this community (Pittsburgh) at least, such is not the case. . . . In the nasal cavities, the vibrissae and turbinates collect a great deal of carbon, which is subsequently removed by the secretions; for, in the examination of nasal polypi and strips of turbinate mucosa removed at operations, we have never seen a single example of free pigment or pigment bearing cells beneath the epithelial layer. . . . In the air passages below the larynx, pigment bearing cells have frequently been observed, but these are either free in the lumen or were surrounded by bits of mucus and other cells and were not found penetrating the epithelial layers. . . . The amount of pigment phagocytosis in the air passages above the lung alveoli must be a negligible quantity. Carbon pigment once taken up by the cells remains intracellular indefinitely unless freed by some process producing general necrosis of the tissues.
>
> The phagocytic cells are not transient scavengers, but in a more leisurely manner gather their pigment load and trans-

4. Haythorn, S. R.: J. M. Res. 29: 259-79, 1913-14.

Digitized by Google

port it to the tissue spaces. The lining cells of the lung alveoli take little or no active part in the phagocytosis of carbon pigment. The process consists in the phagocytosis of the pigment within the lung alveolus by a cell, which is probably an endothelial leukocyte. The cell which takes the early active part in the formation of a tubercle is phagocytic for tubercle bacilli and for pigment granules, and is probably an endothelial cell. The presence of pigment granules within these cells does not interfere with the cells taking part in the formation of a tubercle, in the usual way. The presence of pigment-bearing cells in the connective tissue about tuberculous lesions acts as an additional stimulus to fibrosis and encapsulation. The obliteration of the pulmonary lymph spaces in the anthracotic process is unfavorable for the local spread of tuberculosis, and aids in the localization of the condition. In acute inflammatory conditions where the lymphatics are important for proper resolution, anthracosis becomes seriously detrimental, because of the obliteration of the lymph spaces.

EXPERIMENTAL WORK

Studying the quantitative absorption of dust from air of definite known dust content, Saito [5] found that, in animals, from 4 to 24 per cent. of the total amount of dust inhaled entered the respiratory apparatus, the remainder going into the intestinal tract, being caught in the nose and nasopharynx, and then swallowed. The total retained in the body was about 95 per cent. of the inhaled dust. Sneezing acts as a protection against the accumulation of dust in the animal body. In men,[6] about 2 per cent. or less of white lead powder inhaled through the nose was exhaled again, about 51 per cent. remaining in the nose and 3 per cent. in the mouth; when the powder was inspired through the mouth, about 80 per cent. was retained in the lung. Fluid droplets or solutions of potassium iodid, sodium chlorid or sodium chromate may be absorbed to the extent of 96 per cent.[7] The exact site of absorption was not determined.

A great deal of experimental work has been performed to discover the origin and disposition of the

5. Saito, Yorchiro: Arch. f. Hyg. **75**: 134-51, 1911-12.
6. Lehmann, K. B.; Saito, Yorchiro, and Gfrörer, Walter: Arch. f. Hyg. **75**: 152-9, 1911-12.
7. Lehmann, Saito and Majima: Arch. f. Hyg. **75**: 160-6, 1911-12.

Digitized by Google

characteristic and important epithelioid cell of the tubercle, and the opinions have finally crystallized into the view taken by Foot [8] in his recent studies, which also include experimental studies with India ink (carbon) and pulmonary tuberculosis. His views, which concur with those first expressed by Mallory and by Klotz and Haythorn, are that the epithelioid cell is of definitely endothelial origin. There is little evidence that the local tissue elements take an active part in the process of tubercle formation, until after the lesion is formed; the reaction is, in a sense, exudative, since the lesion is produced from cells which migrate to the site of inflammation. The lymphocyte appears late and is not to be considered as a potential epithelioid cell; its presence in the tubercles is as yet unexplained. Experimental tubercles are formed in the lung primarily by cells originating in the capillary endothelium. These cells are probably present in small numbers in the normal lung, lying free in both the alveolar wall and the air vesicles. In response to infection, they proliferate in the capillary walls in the vicinity of the invading organisms, migrate in steadily increasing numbers, and, arriving at the site of the infection, further multiply, and, to some extent, fuse to form the syncytia known as giant cells. The epithelial cell takes no active part in the process; its proliferation tends to repair denuded surfaces and is regenerative rather than combative or phagocytic in nature. This cell does not take up carbon (particulate matter), in contradistinction to the endothelial cell. The cells of endothelial origin not only phagocytose tubercle bacilli but also carry them into the tissues; for example, into lymph nodes, by way of the lymphatics, or into other lung lobules by way of the air passages, in which they are readily demonstrable.

8. Foot, N. C.: Studies on Endothelial Reaction: II, The Endothelial Cell in Experimental Tuberculosis, J. Exper. Med. **32**: 513 (Nov.) 1920; III, The Endothelial Cell in Experimental Pulmonary Tuberculosis, ibid. **32**: 533 (Nov.) 1920; IV, The Endothelium in Experimental General Miliary Tuberculosis in Rabbits, ibid. **33**: 271 (Feb.) 1921.

Digitized by Google

The conclusions as to the endothelial origin of the phagocytic cells of the lung tissue coincide in every way with those expressed by Permar,[9] colleague of Klotz and Haythorn, who also emphasizes the non-participation of the epithelium in those phenomena of phagocytosis.

Although a great deal has been contributed to the better scientific understanding of the disposition of particulate matter in the lung tissue and lymph glands,[10] certain steps by which this material may gain access to the lower respiratory tract from the upper air passages are still undetermined. It is now generally accepted that anthracosis originates by the aerogenic route of dust inhalation; at least this is the belief expressed in the more recent articles on this and related subjects. That there is direct connection between the various parts of the eye, nasal and oral cavities was brought out with renewed force during the influenza epidemic, in conjunction with studies regarding the use of the gauze mask.

Corper and Enright[11] found that although the greater part of particulate matter (India ink and bacillus prodigiosus) entering by way of the eye is subsequently swallowed and passes into the gastro-intestinal tract, a small but definite portion of it finds its way into the larynx and trachea, where it may persist even as long as a week. In its passage from the eyes, the material traverses a definite channel, dependent on which eye it has entered or into which it has been introduced, being found on the corresponding side of the nasopharynx and tonsil. Infectious material that is ingested is far less likely to enter the respiratory

9. Permar, H. H.: An Experimental Study of the Mononuclear Phagocytes of the Lung, J. M. Res. **42**: 9 (Sept.) 1920, and The Development of the Mononuclear Phagocyte of the Lung, ibid. **42**: 147 (Nov.-Jan.) 1920-1921.

10. Gardner, L. U.: The Relatively Early Lesions in Experimental Pneumoconiosis Produced by Granite Inhalation and Their Influence on Pulmonary Tuberculosis, Am. Rev. Tuberc. **4**: 734 (Dec.) 1920. Willis, H. S.: Studies on Tuberculous Infection, Spontaneous Pneumoconiosis in Guinea-Pigs, Am. Rev. Tuberc. **5**: 189 (May) 1921.

11. Corper, H. J., and Enright, J. J.: The Eye as a Portal of Infection in Respiratory Diseases, J. A. M. A. **74**: 521 (Feb. 21) 1920.

Digitized by Google

tract than that entering by way of the eye. More recently, Bloomfield,[12] in studying the dissemination of bacteria in the upper air passages, found that sarcina lutea or charcoal particles implanted on various areas in the mouth and pharynx adhered at the site of inoculation. The ingestion of a large glass of water following inoculation did not seem to remove more than a very few of the organisms. Whatever the number removed, such organisms were swallowed with the ingested fluids, and not reimplanted on other parts of the mouth or throat, save for an occasional colony. Organisms inoculated on one side of the tongue traveled along the same side with practically no spread across the midline; organisms inoculated on the tonsil or pharynx did not come forward into the mouth.

In 1920, an article appeared by Mullin and Ryder,[13] which detailed the surprising ease with which fluid suspensions of carbon and tubercle bacilli dropped into the noses of rabbits entered the lungs. "The technic was simple as possible. The rabbit was held, usually on its back, with the nose elevated, and about 1 c.c. of India ink or bacterial emulsion allowed to flow into one nostril from a pipet inserted just far enough to insure the fluid entering the nose." Thus, they obtained almost entire blackening of the upper lobes of the lungs, with many black spots irregularly distributed over the rest of the lungs, especially when the ink was given a number of times. The tuberculosis obtained in the same way had involved the upper and middle lobes when the rabbits were killed after seven weeks.

In the hope of being able to utilize the intratracheal route for the more direct application of therapeutic agents in pulmonary inflammatory conditions, and to elucidate certain phases of pulmonary edema, Winter-

12. Bloomfield, A. L.: Am. Rev. Tuberc. **5**: 903, 1922; Bull. Johns Hopkins Hosp. **33**: 145, 1922.
13. Mullin, W. V., and Ryder, C. T.: Am. Rev. Tuberc. **4**: 683 (Nov.) 1920.

Digitized by Google

nitz and Smith [14] studied the absorption of fluids from the lungs and found that high quantities of fluid can be introduced through the trachea without untoward effects. In acute inflammatory processes, fluid in the pulmonary parenchyma may be a means of disseminating the infection through the lung tissue. A considerable period of time may be necessary before fluid (isotonic salt solution) introduced into the alveoli of the lung is entirely absorbed. After eighteen hours, much has disappeared, and within four days it has been absorbed without a trace. Inert foreign material can be washed out by the method of intratracheal pulmonary irrigation; but even after prolonged treatment of this kind, in which many liters of irrigating fluid are employed, there is still a residue of the original material introduced. A nonlethal dose of virulent pneumococci introduced into the lungs of rabbits, followed by irrigation, resulted in a very diffuse and fulminating lobar consolidation. Irrigation with salt solution not only cannot be utilized to advantage, but is actually a disseminator and an aggravator of the inflammatory process within the lung.

Even though histologic studies of the distribution of aspirated fluids containing particulate matter were not available, roentgenologic studies in experimental animals have been recorded. In 1917 Waters, Bayne-Jones and Rowntree [15] forcibly injected into the trachea of dogs a 10 per cent. suspension of iodoform in olive oil, under ether anesthesia with the animal lying on its abdomen. Dissection showed the material apparently in the same degree of suspension in the bronchi, bronchioles and smallest air passages. Microsections showed large masses of fat filling the alveoli. The position of the catheter in the trachea determined somewhat the distribution of the fluid. The plates revealed that the bronchioles of the upper lobes and the alveoli of the

14. Winternitz, M. C., and Smith, G. H.: Contributions to Medical and Biological Research, Osler Memorial **2**: 1255, 1919.

15. Waters, C. A.; Bayne-Jones, S., and Rowntree, L. G.: Roentgenography of the Lungs, Arch Int. Med. **19**: 538 (April) 1917.

Digitized by Google

apexes were filled when the injection was made into the lower third of the trachea. The mixture produced a proliferative broncho-pneumonia.

In view of the belief of Klotz and his coworkers that carbon enters the lung parenchyma only through the alveoli, it seems well to call attention to the fact that bacteria may act slightly differently at times, since Winternitz, Smith and Robinson [16] have found that pneumococci can enter the tracheal lymphatics through a damaged epithelium and spread by way of the lymphatics to the lung. The lymphatics of the submucosa of the trachea afford a direct pathway of infection to the lung. The submucosa of the trachea contains a rich plexus of lymphatics, prominent everywhere and devoid of valves. Although this lymphatic system provides a pathway for infection, it may also serve as a protective mechanism against pulmonary infection; for the drainage of the submucosa of the trachea and bronchi is largely diverted as the lung is approached to the protecting regional lymph glands. They divide the pneumonias into two groups: those secondary to damage of the protective mechanism of the upper respiratory tract, and those in which such damage was not demonstrable. No explanation has been suggested for the latter, except that the pathway of the microorganisms was through the lumen of the trachea and bronchi.

Realizing that there were certain gaps in the steps by which inhaled dry or aspirated liquid particulate matter reached the lung parenchyma, information which might eventually suggest a means of applying therapeutic agents to the lung, experiments were undertaken to follow if possible the immediate result of the inhalation of soot, and inspiration or aspiration of India ink (fluid). Regarding the inhalation of soot for either short or long periods of time, microscopic examination

16. Winternitz, M. C., Smith, G. H., and Robinson, E. S.: Bull. Johns Hopkins Hosp. **31**: 63 (March) 1920.

Digitized by Google

revealed that it was rather irregularly deposited in the air passages, and that marked accumulations occurred, especially on the elevations or projections seen at the bifurcations of the smaller and larger divisions of the respiratory passages. In distinction to this, the alveoli were comparatively free from the inhaled crabon particles. Its final deposition around miliary tubercles also occurred irregularly, some being surrounded with heavy deposits of carbon and others being fairly free from such deposits; so that an inhalation therapy with particulate matter suspended in the respired air would not at present seem feasible in pulmonary tuberculosis.

Liquids inspired or aspirated into the lung showed an entirely different histologic distribution, the tendency being toward an immediate aspiration into the alveoli, where the particulate matter was retained for a comparatively long time. If deposit was retained in the bronchi and bronchioles, this would be found lying along the walls, and not accumulated at the bifurcations, and on projections seen histologically as noted with the dry inhaled smoke or soot. While inhaled soot appeared macroscopically to be fairly uniformly disseminated throughout the entire lungs although irregularly as to the finer histologic distribution, inspired or aspirated fluid (India ink) was more patchy in its localization, which, however, conformed to certain definite laws dependent on the posture of the animal at the time of inspiration of the fluid. In rabbits in the horizontal posture, with head slightly elevated, repeated nasal instillations of small amounts of India ink, from 1 to 3 c.c., failed to enter the trachea or lungs. When, however, the animals were held in the vertical posture and the ink dropped into the nose, even after one instillation it was visible in the lungs, usually being confined to the lower lobes. Under ether anesthesia, with the rabbit in the horizontal posture and the head slightly elevated, an instillation of India ink would readily enter the lungs; but the distribution

Digitized by Google

differed from that seen in the vertical posture in that the greater part was confined to the upper lobes. The distribution was also dependent on the side on which the rabbit was lying during the instillation. If the animal lay on the right side, the ink was confined mainly to the right upper lobe; if on the left side, to the left upper lobe.

The postural distribution was also borne out in dogs, although access to the lung was more difficult without anesthesia in that it required an immediate administration of rather large amounts of India ink (from 10 to 20 c.c.) to attain results in the vertical posture, and then only relatively small amounts were inspired into the lungs, mostly into the lower lobes. With the animal under ether anesthesia, however, and in the horizontal posture, aspiration was easily accomplished, the ink being confined mostly to the upper lobes and to the side on which the animal was lying. These results were also repeated in the main in an artificial imitation of the chest, in which a fresh rabbit lung was suspended in a large wide mouthed bottle, the trachea connected with a dropping funnel containing India ink. Through a second hole entering the stopper of the bottle, a glass tube was connected with a suction pump to produce the inspiratory negative pressure occurring in the pleural spaces. The bottle could be laid in any position to imitate the various postures of the animal. From these experiments it seems highly probable that the disposition of the inspired fluid is dependent entirely on a mechanical mechanism, gravity and inspiratory suction. A study of sections from the lungs of animals permitted to aspirate India ink also indicates that the solid particles of the ink which had reached the alveoli were to a great extent retained in them even after three months. In one animal that had inspired India ink from the nose eleven days prior to section, a typical lung abscess was found in the posterior portion of the lung even though the animal was not ill.

Digitized by Google

By utilizing the information gained from the experiments with India ink, typical upper lobe pulmonary tuberculosis was produced in dogs by instilling heavy suspensions of dead human and bovine tubercle bacilli in saline solution into the nose, with the head slightly elevated, while the animal was under ether anesthesia. Right or left side upper lobe involvement was produced at will by merely placing the animal on the right or left side during the nasal instillation. The tuberculous involvement resembled the typical upper lobe type found in man, except that cavitation did not occur with the dead bacilli. Typical fibrotic pleural and interlobar adhesions were found, and histologically the tissues presented the typical granulation tissues of tuberculosis, with necrosis evident in locations.

These experiments are significant in that they throw light on the importance of posture during anesthesia, especially in avoiding the quick and ready access of infectious material which is aspirated from the upper air passages to the finest divisions of the lungs, the alveoli, which act in the manner of traps, where it may be retained for a long time, to cause subsequent tissue changes. If we are to accept the more recent conclusions on lung abscess, which indicate that direct aspiration is the more important mode of infection, and this seems to be the trend of the times, it behooves the surgeon and anesthetist to improve by consideration of posture the means and methods of administering anesthetics, especially in operations on the upper respiratory tract. Moore [17] calls attention to the danger of the semirecumbent and upright positions during anesthesia, which the foregoing studies bear out.

The experiments also seem to indicate that the present mode of treating pulmonary hemorrhage can be placed on a more scientific basis by consideration of posture as a factor in promoting hemostasis in the

17. Moore, W. F.: Pulmonary Abscess: An Analysis of Two Hundred and Two Cases Following Operative Work About the Respiratory Passages, J. A. M. A. **78**: 1279 (April 29) 1922.

Digitized by Google

bleeding lung; not to mention that there is a possible connection between posture and the intrapulmonary dissemination in the open ulcerative type of tuberculosis. Although dead tubercle bacilli have been used, for obvious reasons, in the experiments cited, and a nonprogressive pulmonary tuberculosis, confined mainly to the upper lobes, resembling that seen in man, was produced, it seems justifiable to infer that, by using living virulent bacilli in the same manner and with proper safeguard for the worker, the disease can be reproduced in dogs and other animals, presenting all the clinical characteristics of pulmonary tuberculosis in man, with massive acute pneumonic consolidation or ulceration and cavity formation suitable for all types of experimental therapy, surgical and medicinal. Further studies on the aspiration of fluids both from extra and from intrapulmonary sources may also elucidate the many vague conceptions as to the mode and spread of intrathoracic diseases.[18]

SUMMARY

The immediate intrapulmonary distribution of inhaled particulate matter (smoke or soot) differs from that of the inspiration or aspiration of particulate matter suspended in fluids (India ink). The former is found heaped up at the points of bifurcation of the air passages or on any prominent projections, as seen in the histologic sections, with relatively little being retained in the alveoli; while the inspired fluid quickly reaches the alveoli, where the insoluble particles of it are retained for a comparatively long time by the trap-like action of these terminal air vesicles. While the inhaled particles are fairly uniformly distributed throughout the entire lung, the inspired or aspirated fluid is irregularly distributed, and its location is determined to a great extent by posture. The pulmonary inspiration or aspiration of fluids after nose instillation

18. The complete report of these experiments will appear elsewhere.

Digitized by Google

occurs readily in dogs and rabbits under ether anesthesia, and in the horizontal posture with the head slightly elevated. The inspired fluid is confined to the upper lobes of the lungs and to the side on which the animal lay, while without anesthetic, repeated nose instillations are usually unsuccessful in this posture. In the vertical posture, however, the inspiration of fluids into the lungs is easily attained in rabbits, but less so in dogs, without anesthetic, the fluid being found mainly in the lower lobes. The postural distribution can be imitated in an artificial chest, indicating that it is determined by mechanical means, gravity and inspiration or aspiration. By utilizing the postural data, right or left side upper lobe pulmonary tuberculosis, possessing many of the characteristics of the disease in man as to location, the formation of pleural adhesions, tissue granulation and necrosis, can be reproduced in dogs, by the nasal instillation of suspensions of tubercle bacilli while the animal is under ether anesthesia and lying on the right or the left side during the operation.

3800 East Colfax Avenue.

Digitized by Google

STUDIES ON THE RELATION OF THE THYROID TO PANCREATIC DIABETES IN DOGS

WITH SUGGESTIONS AS TO DIABETES MELLITUS IN MAN *

GEDIDE A. FRIEDMAN, M.D.

AND

JULIUS GOTTESMAN, M.D.

NEW YORK

Little doubt as to the pancreatic origin of diabetes mellitus remains, since Weichselbaum [1] demonstrated, by special staining methods in all diabetics from his large necropsy material, definite changes in the islands of Langerhans, and since Cecil [2] noted similar changes at necropsies in seventy-nine of his ninety diabetics.

The fact, however, that glycosuria and hyperglycemia may be transient in some persons favors the assumption that anatomic changes in the islets must not necessarily be present in mild cases of the disease. Emotional causes may lead in some persons to a transient glycosuria, especially in those with a congenital inferiority of the pancreas. A temporary disturbance in the insular apparatus also occurs during infections, as in the course of chronic cholecystitis. Various drugs also may have this effect. Last but not least, certain endocrine disorders, such as hyperpituitary and hyperthyroid states, will occasionally lead to glycosuria and even to true diabetes mellitus. As actual pathologic changes in the islands were hardly ever found in

* From the Department of Clinical Pathology, College of Physicians and Surgeons, Columbia University.

1. Weichselbaum, quoted by Pratt, J. H.: Internal Function of Pancreas, J. A. M. A. **59**: 322 (Aug. 3) 1912.

2. Cecil, R. L.: A Study of the Pathological Anatomy of the Pancreas in Ninety Cases of Diabetes Mellitus, J. Exper. Med. **11**: 266, 1909.

Digitized by Google

acromegaly and in exophthalmic goiter, one must assume that in these maladies the insular apparatus is disturbed functionally.

The relationship between thyroid diseases and diabetes mellitus was first pointed out by Dumonptallier [3] in 1867. He described a case of exophthalmic goiter and diabetes in a young woman. Since that time similar cases have been reported from time to time. However, Fitz [4] and Sainton [5] and his associates emphasize the rarity of the two maladies combined in one person, and both consider such a combination as a mere coincidence. Holst [6] reports eight cases of exophthalmic goiter with not only alimentary but also spontaneous glycosuria, including three cases which must be considered as a combination of exophthalmic goiter and diabetes. From this and other data cited in his paper, he draws the conclusion that tests for sugar should be applied as a routine measure in cases of hyperthyroidism, and that diabetic patients should always be examined for hyperthyroid symptoms.

Although every clinician will admit that spontaneous glycosuria, as well as fasting hyperglycemia, are rare occurrences in hyperthyroid states, yet alimentary glycosuria in the latter conditions may be considered as common. Low sugar tolerance was reported by Denis [7] and her associates in all their cases of hyperthyroidism, and recently it was corroborated by Morris [8] and others. It is also a well established fact that, in true myxedema, the assimilation limit for dextrose is high. Experimentally, it was shown by McCurdy [9] and others that

3. Dumonptallier: Goitre exophthalmique et glycosurie chèz la même malade, Compt. rend. Soc. de biol. **4**: 116, 1867.
4. Fitz, Reginald: The Relation of Hyperthyroidism to Diabetes Mellitus, Arch. Int. Med. **27**: 305 (March) 1921.
5. Sainton, P.; Schulmann, E., and Justin-Besançon: Bull. et mém. Soc. méd. d. hôp. de Paris **45**: 1298 (July 29) 1921.
6. Holst, J.: Glycosuria and Diabetes in Exophthalmic Goiter, Acta med. Scand. **55**: 302 (June) 1921 (in English); abstr. J. A. M. A. **77**: 744 (Aug. 27) 1921.
7. Denis, W.; Aub, J. C., and Minot, A. S.: Blood Sugar in Hyperthyroidism, Arch. Int. Med. **20**: 964 (Dec.) 1917.
8. Morris, M. F., Jr.: Value of the Alimentary Test in the Diagnosis of Mild Hyperthyroidism, J. A. M. A. **76**: 1566 (June 4) 1921.
9. McCurdy, J.: Influence of Thyroidectomy on Alimentary Glycosuria, J. Exper. Med. **11**: 798, 1909.

Digitized by Google

dextrose tolerance was high in thyroidectomized dogs, and if the parathyroids were preserved, the results were permanent. This does not exist in hypothyroid conditions. Garrod [10] refers to the occurrence of glycosuria and even of true diabetes in subthyroid persons. From these considerations one is justified in concluding that, while thyroid overactivity does not lead to definite pathologic changes in the insular apparatus, it leads to a functional disturbance in the latter, as evidenced from the low sugar tolerance in hyperthyroid states. The high sugar tolerance in athyroid conditions must be credited with a functional disturbance of reverse nature. Various degrees of thyroid hypo-activity do not suffice to upset the islands of Langerhans in the same manner as in myxedema.

It is but logical to assume that a functional disturbance in the thyroid may be a possibility in diabetes mellitus. We speak of a functional disturbance of the pancreatic islets in exophthalmic goiter and of a similar disturbance of the thyroid in diabetes because a thorough search through the literature does not reveal sufficient data as to the actual pathologic condition of the pancreas in the former condition, nor to thyroid changes in the latter. Garrod,[10] while stating that glycosuria may exist in conjunction with thyroid deficiency, admits knowledge of a few cases in which exophthalmic goiter was associated with atrophy and other lesions of the pancreas. According to Holst,[6] in nine cases of exophthalmic goiter recorded, the pancreas was pathologic. Just as little is known about thyroid changes in diabetics. Cecil [11] writes that adenoma of thyroid glands has been noted in the anatomic diagnosis of two cases of diabetes. But it is rather strange that in these cases the pancreatic islets were hyperthophied, a seemingly paradoxical histologic picture of the pan-

10. Garrod, A. E.: Glycosuria, Lancet, March 9, 1912.
11. Cecil, R. L.: The Effect of Certain Experimental Procedures on the Islands of Langerhans, J. Exper. Med. **16**: 1, 1912.

Digitized by Google

creas in diabetics, though described by MacCallum [12] and others. Kraus [13] speaking of the changes in the pars media of the hypophysis in diabetes mellitus, cites several cases in which the pathologic picture of the thyroid was interpreted by him as corresponding to overactivity of the thyroid. Few investigators studied the thyroid microscopically in depancreatized dogs. Lorand [14] asserts that the histologic picture of the thyroid in diabetic dogs must be interpreted as overactivity. Licini [15] described the thyroid in experimental diabetes as presenting the colloid type, which may occasionally be seen in exophthalmic goiter. He emphasizes overactivity of the thyroid in his dogs and states that endemic goiter did not exist in the locality from which his animals were procured.

Pratt [16] is rather careful in commenting on the histologic picture of the thyroids in his depancreatized animals. The glands of three dogs, in whom pancreatic insufficiency without glycosuria had existed from five to thirty-four months, presented the normal size, color and consistency. The histologic study, however, revealed either a partial or total disappearance of colloid, and in its place were desquamated epithelial cells, so numerous as to fill many of the alveoli. The cells varied in size, but large ones predominated. The nuclei took the stain deeply and uniformly. Pratt is in doubt as to whether the changes he discovered indicate a compensatory action on the part of the thyroid or whether they presented merely a degenerative state.

As the histology of the thyroid in our depancreatized dogs will be referred to in another paper, it should be stated here that there is no uniform histologic picture,

12. MacCallum, W. G.: Hypertrophy of the Islands of Langerhans in Diabetes Mellitus, Am. J. M. Sc., March, 1907.
13. Kraus, E. J.: Hypophyse und Diabetes Mellitus, Virchows Arch f. path. Anat. **228**: 68-133, 1920.
14. Lorand, A.: Les rapports du pancreas (Islets of Langerhans) avec la thyroide, Compt. rend. Soc. de biol. **56**: 488-490, 1904.
15. Licini, C.: Einfluss der Exstirpation des Pancreas auf die Schilddrüse, Deutsch. Ztschr. f. Chir. **101**: 4, 5 and 6, 1909.
16. Pratt, J. H.: (Footnote 1).

Digitized by Google

even in exophthalmic goiter. Kocher [17] and Marine [18] have described three types in this malady: the hyperplastic, the colloid, and the hyperplastic and degenerative. It may also be mentioned that sufficient information cannot be obtained by studying thyroids from depancreatized dogs microscopically. The determination of the iodin content of the thyroids of depancreatized animals may lead to a better understanding of the part taken by the thyroid in diabetes mellitus. Such investigation has been started by us.

From all the considerations of the relationship of the thyroid to the pancreas, two statements may be considered as absolutely certain: that overactivity of the thyroids leads to a lowering of the assimilation limit of dextrose, and that complete atrophy of the gland raises it. Myxedematous persons are not likely to become diabetic.

It is highly probable that the difference in the severity of the clinical course in diabetes mellitus at various ages depends in a measure on the difference, with age, in the physiologic functioning of the thyroid. In infancy, the epithelium of the thyroid is of a columnar type, according to Marine,[19] Kocher [20] and Jackson,[21] in adolescence the epithelium is cubical, and in elderly persons, flat. It is well known that diabetes takes a very severe course in children; the disease is severe in adults but extremely mild when acquired in old age. The mortality from diabetes mellitus in children is almost 100 per cent., in spite of advanced modern treatment; and if Riesman [22] has observed several cures

17. Kocher, Albert: Die histologische und chemische Veranderung der Schilddrüse, Virchows Arch. f. path. Anat. **208**: 86-296, 1912.

18. Marine, David, and Lenhart, C. H.: Pathologic Anatomy of Exophthalmic Goiter, Arch. Int. Med. **8**: 265 (Sept.) 1911.

19. Marine, David, quoted by Jackson, C. M.: Effects of Inanition on Structure of Thyroid and Parathyroid Glands of Albino Rat, J. Anat. **19**: 305 (March) 1916.

20. Kocher, Albert: Morbus Basedowii, in Kraus und Brugsch: Specielle Pathologie und Therapie innerer Krankheiten, Berlin and Vienna, Urban and Schwarzenberg **1**: 909, 1919.

21. Jackson, C. M.: (Footnote 19).

22. Riesman, D.: Mild Diabetes in Children, Am. J. M. Sc. **151**: 40-44 (Jan.) 1916.

Digitized by Google

in children, he himself admits that the diabetes in them was of renal origin. The mortality from diabetes is still high in adolescence.

It seems, then, that the tendency of the thyroid to physiologic atrophy may be the determining factor for the mild course of diabetes in elderly persons. The absence of diabetes in true myxedema and the mild course of diabetes in advanced age are suggestive of a cure for diabetes by inducing a complete atrophy of the thyroid. If this is true, it would be reasonable to assume that a spontaneous cure of diabetes is occasionally possible through an atrophic state of the gland, brought about by unknown causes.

In connection with this point of view, one of Rohdenburg's [23] cases may be cited:

A Russian Jewess, aged 45, married and having five children, was examined for insurance when 30 years of age, and sugar was discovered in the urine. Treatment was of no avail. The menopause was very stormy from 39 to 41. After this, it was accidently discovered that the sugar had disappeared. The patient was then able to eat candy with impunity. Death occurred at the age of 45 with what resembled chronic nephritis, though it was evident that there was also myxedema. The necropsy revealed almost complete fibrosis of the thyroid, fibrosis of the major portion of the head of the pancreas, hypertrophy of the islands of Langerhans in the middle portions, a normal pancreatic tail, marked arteriosclerosis, and marked interstitial nephritis.

As true myxedema is hardly ever combined with diabetes mellitus; as the course of diabetes is mild in elderly persons, and since a spontaneous cure of the disease is possible through atrophy of the thyroid, the possibility of observing the disappearance of glycosuria in depancreatized dogs, either after ligation of all thyroid arteries, or after removal of the thyroid gland in toto, suggested itself to us. One could not expect to observe an increase in weight of depancreatized animals after these procedures, as it is well known that total or

23. Rohdenburg, G. L.: A Case of Spontaneous Disappearance of Diabetes, Endocrinology 6: 519 (July) 1922.

Digitized by Google

nearly total extirpation of the pancreas leads to enormous losses in body weight in every case.

At the present stage of our knowledge, we do not possess means to destroy only the insular apparatus of the pancreas, leaving the external secretory apparatus intact; so one can imitate human diabetes only to some extent by the experiment. Complete removal of the pancreas always leads to glycosuria and hyperglycemia. To produce glycosuria after partial pancreatectomy, one must remove a little more than 2 gm. for each kilogram of body weight of the animal in the majority of cases. While one may occasionally succeed in obtaining persistent glycosuria by removing less than this amount, hyperglycemia without glycosuria manifests itself almost always after removal of small amounts of pancreatic tissue.

Of fifty dogs which we depancreatized from January, 1921, to May, 1922, persistent glycosuria became evident after removal of 1.3 gm. in one dog and, in another, after extirpation of 1 gm. per kilogram of body weight. As the latter animal's digestion did not suffer from a lack of pancreatic ferments, we believe that, by chance, we imitated true human diabetes. This information is by no means new since, in the literature on experimental diabetes, reports have frequently appeared pertaining to induction of diabetes in dogs by removal of comparatively small amounts of pancreatic tissue.

The duration of life in diabetic dogs, after complete thyroidectomy, is greatly shortened, as is evidenced by the experiments of Lorand, MacCallum and Eppinger, quoted in a previous paper.[24] Our own diabetic dogs in which the thyroid was removed in one sitting also died in from two to three days after thyroidectomy. Complete ligation of the thyroid arteries, or, better still, partial ligation followed at a later date by complete

24. Friedman, G. A., and Gottesman, Julius: Relation of Thyroid and Parathyroids to Pancreatic Diabetes in Dogs, Proc. Soc. Exper. Biol. & Med. **19**: 215-221, 1922.

Digitized by Google

thyroidectomy, enabled us to keep the animals alive for a longer period of time, and greatly extended the time of observation.

Recently we performed thyroidectomy in hyperglycemic dogs in two sittings, but during the second lobectomy we left a tiny piece of the thyroid tissue in situ. In performing a thyroidectomy, one only occasionally succeeds in sparing all parathyroids, so that tetany ensues. The occurrence of tetany is less frequent after total ligature of the vessel than after thyroidectomy.

Diabetic dogs are more liable to be affected by tetanic seizures with two or three parathyroids left in situ, than are nondiabetic dogs with the same number of parathyroids.

During the time of observation, all the dogs were on the routine laboratory diet, consisting of bread, meat and carrots. Blood sugar estimations were made by the Lewis and Benedict method, by Miss Helen Emmons.

RESULTS OF EXPERIMENTS

Ligation of all thyroid arteries in completely or almost completely depancreatized dogs leads to the disappearance of sugar from the urine in from one to five days after ligation, provided tetany or infection does not occur. Parallel with the disappearance of the sugar, the blood sugar greatly diminishes or may become normal.

Partial ligation of the thyroid arteries does not lead to cessation of glycosuria, and the blood sugar may even become increased.

Total thyroidectomy which is preceded by partial ligation of the arteries leads to the disappearance of sugar, provided tetany does not occur. If, however, mild attacks of tetany set in, the glycosuria does not cease. But when one succeeds in checking the tetanic seizures completely, by intravenous injections of calcium lactate, the sugar in the urine disappears entirely,

Digitized by Google

and reappears when tetany sets in again. Parallel with the disappearance of sugar in the urine, the blood sugar greatly diminishes and becomes normal.

If a small amount of pancreatic tissue is removed in order to cause hyperglycemia, one-sided thyroidectomy does not diminish the blood sugar content; and if, in removing the second lobe, a tiny fragment of thyroid is left, the blood sugar may become normal temporarily, but later it becomes high. These dogs with high blood sugar gain in weight and remind one of human beings in the prediabetic state.

If one succeeds in causing diabetes in a dog by removing a comparatively small amount of pancreatic tissue, 1 gm. per kilogram of body weight, and succeeds also in sparing all the parathyroids of the animal in performing a thyroidectomy, the glycosuria which has not ceased after partial ligation of the arteries ceases after removal of the thyroid.

ABSTRACTS FROM PROTOCOLS OF SOME EXPERIMENTS PERFORMED IN 1921

LIGATION OF ALL THYROID ARTERIES IN DEPANCREATIZED DOGS

EXPERIMENT 1 (Dog 4).—Complete pancreatectomy was performed, March 2. The urine was positive for sugar from the day following operation in amounts varying from 5 to 6 per cent. Ligation was effected, March 5. The dog continued to have sugar in the urine until March 8. The urine became sugar free, March 9, and continued to be sugar free in passed and catheterized specimens until March 19, when the dog developed distemper, which was followed by death on the next day. Necropsy revealed lobular pneumonia involving all lobes and complete absence of pancreatic tissue.

EXPERIMENT 2 (Dog 15).—Complete pancreatectomy was performed, June 22. There was glycosuria from June 23 to June 28. Ligation was effected, June 28. The urine was sugar positive, June 29, and sugar negative on daily examinations of passed and catheterized specimens from June 30 to July 13. The animal was found dead, July 14. Necropsy revealed no demonstrable lesions. The dog had a good appetite until July 12.

EXPERIMENT 3 (Dog 10).—Complete pancreatectomy was performed, June 29. There was glycosuria from June 30 to July 5. Ligation was effected, July 5. The urine was strongly

Digitized by Google

positive for sugar, July 6, but there was no trace of sugar in the urine, July 7. There was glycosuria from July 8 to July 14. Twitching of the musculature of the back took place from July 8 to July 10. July 11, the dog had a severe attack of tetany. July 12, he had mild attacks of tetany. Infection at the neck was noted. The dog was killed with chloroform, July 14. Necropsy revealed a large pocket of pus at the neck.

EXPERIMENT 4 (Dog 16).—Almost complete pancreatectomy was performed, July 25. There was glycosuria from July 27 to July 30. Ligation was effected, July 30. Glycosuria persisted until August 6, when the animal was found dead. There was no necropsy. During the course of the experiment, no tetany was noted. Infection at the neck was noted, August 3, four days after ligation.

EXPERIMENT 5 (Dog 9).—Almost complete pancreatectomy was performed, April 3. There was glycosuria from April 4 to April 10. The superior and inferior thyroid arteries on the right side were ligated. Glycosuria persisted on daily examinations. The superior and inferior thyroid arteries on the left side were ligated, April 17. The urine was sugar positive, April 18. The dog died on the next day from a severe attack of tetany. The animal was in good condition until the day after the second ligation. No necropsy was performed.

COMPLETE THYROIDECTOMY PRECEDED BY LIGATION OF INFERIOR THYROID ARTERIES IN DEPANCREATIZED DOGS

In these experiments, two or three parathyroids were left in situ, and all were left in one dog.

EXPERIMENT 6 (Dog 17).—Partial pancreatectomy was performed, November 9. Glycosuria was noted from the 10th to the 16th. Ligation was effected, November 16. Glycosuria persisted from the 17th to the 30th. Thyroidectomy was performed, December 1. There was not a trace of sugar in the urine, December 2. Glycosuria followed, and the dog developed a severe attack of tetany early in the morning and died in the afternoon. Necropsy did not reveal demonstrable lesions.

EXPERIMENT 7 (Dog 14).—Partial pancreatectomy was performed, December 3. There was glycosuria from the 5th to the 7th. Ligation was effected, December 7. Glycosuria persisted until the 10th. Thyroidectomy was performed, preceded by intravenous injections of 10 c.c. of 5 per cent. calcium lactate solution. Three parathyroids were left in situ. There was glycosuria, December 12 and 13. Twitching of the musculature of the back was noted. Fifty cubic centimeters of 5 per cent. solution of calcium lactate was administered through a stomach tube. December 14, the dog

Digitized by Google

had a severe attack of tetany early in the morning. At 11 a. m. calcium lactate was injected intravenously in the same dosage as preceded the operation. The animal recovered from the attack, but twitchings persisted. At 2 p. m., he had another attack and was in a dying condition. At 3 p. m., calcium lactate in the same dosage was injected. The dog was catheterized twice, and on both occasions a positive test for sugar in the urine was obtained by adding two drops to Benedict's solution. December 15 and 16, the animal completely recovered from the attack, had an excellent appetite and ate plenty of bread and meat. There was not a trace of sugar in the catheterized and passed specimens of urine, according to tests made with Nylander's and Benedict's reagents. On the 17th, 18th and 19th, twitchings were seen but there were no severe attacks; sugar in the urine was strongly positive. On the 20th, the dog had a severe attack of tetany. Sugar in the urine was strongly positive. Calcium lacate was injected intravenously in the morning and in the afternoon. December 21 and 22, tetany was completely absent. The urine was sugar free on these days. December 23, the dog was bitten in the back by another dog. On account of the large open wound, he was killed.

EXPERIMENT 8 (Dog 19).—Partial pancreatectomy and ligation of inferior thyroid arteries was performed, December 17. Glycosuria was noted from the 18th to the 21st. Thyroidectomy was performed, December 21. Glycosuria was noted from the 23d to the 25th, and twitching of the musculature of the back was noted on the day following removal of the thyroid. This persisted, although daily subcutaneous injections of calcium lactate, in the same dosage as the intravenous injections, were given. The animal vomited with blood, December 24 and 25, and was found dead, December 26. Necropsy revealed no pneumonia, but the stomach was filled with blood. No food was present. The mucosa of the pylorus was covered with numerous hemorrhagic erosions.

EXPERIMENT 9 (Dog 28).—On a male dog, weighing 14 kg., partial pancreatectomy was performed, January 12. He became glycosuric on the day following the removal of about 1 gm. of pancreatic tissue per kilogram of his body weight. Seven days after there was from 2 to 3 per cent. of sugar in the urine. Both inferior thyroid arteries were ligated. The glycosuria persisted on daily examinations. Seven days later, both lobes of the thyroid were removed; all the parathyroids were spared. There was not a trace of sugar in the urine on the day following thyroidectomy, and the urine remained sugar free for 108 days, although eleven days after removal of the thyroid, additional pancreatic tissue was removed, and ninety-three days after the second pancreatectomy, the last remnant of the gland was taken out. The animal was sugar free for four days after the third pancreatectomy. He died on the fifth day from prolapse of the

Digitized by Google

intestine, which was probably brought about by the three laparotomies. The dog's condition was excellent throughout; he ate well until the day of the accident. He did not show signs of myxedema during the time of observation, and while his original weight was 14 kg., his weight on the day before death was 15.9 kg., a gain of 1.9 kg. The blood sugar remained normal, and fourteen days after removal of the thyroid, the sugar tolerance was about 10 gm. per kilogram of the body weight.

ABSTRACTS FROM PROTOCOLS OF EXPERIMENTS PERFORMED IN 1922

Thyroidectomy was performed in one or two sittings in depancreatized hyperglycemic dogs which at no time showed glycosuria. Three parathyroids were spared in all of them.

EXPERIMENT 10 (Dog 20).—Partial pancreatectomy was performed, February 2. Hyperglycemia was noted, and a second pancreatectomy was performed, February 20. Hyperglycemia increased. Right-sided lobectomy was performed, February 27. Hyperglycemia persisted. Left-sided lobectomy was performed, March 13. The animal died, March 17, from an acute attack of tetany.

EXPERIMENT 11 (Dog 27).—Partial pancreatectomy was performed, April 9, followed by hyperglycemia. Right-sided lobectomy was performed, April 22. Hyperglycemia increased, and left-sided lobectomy was performed, April 29. In the morning of May 1, the animal had a severe attack of tetany. The dog recovered after subcutaneous injection of calcium lactate, but died in the afternoon from tetany.

EXPERIMENT 12 (Dog 23).—Partial pancreatectomy was performed, March 8, followed by hyperglycemia. After removal of both thyroid lobes, March 19, blood sugar was normal, March 20. Tetany manifested itself March 21, and was checked by intravenous injections of calcium lactate. The animal was free from tetany from March 21 in the afternoon until March 25, when it suddenly developed tetany and was killed with chloroform. The blood sugar was normal on the afternoon of March 21 and on two examinations, March 22.

EXPERIMENTS ON DEPANCREATIZED HYPERGLYCEMIC DOGS

In these animals, when the second lobectomy was performed, a tiny fragment of thyroid tissue was left; also three parathyroids were spared.

EXPERIMENT 13 (Dog 24).—Partial pancreatectomy was performed, March 15, followed by hyperglycemia. There was hyperglycemia after right-sided lobectomy, March 25. After left-sided incomplete lobectomy, April 1, there was a tendency of the blood sugar to become normal, but it ultimately remained high. There was considerable gain in weight, which was

Digitized by Google

originally 9 kg., March 25; ten days after pancreatectomy, it was 8 kg.; May 8, it was 11.6 kg.

EXPERIMENT 14 (Dog 25).—The pancreatic tail was removed, April 2. There was hyperglycemia. Right-sided lobectomy was performed, April 15. There was hyperglycemia. An incomplete left-sided lobectomy was performed, April 23. At the beginning, the blood sugar became normal, but later it increased and remained high. There was a gain in weight, which was originally, 7 kg., and May 8, 7.6 kg.

EXPERIMENT 15 (Dog 26).—Partial pancreatectomy was performed, April 8. There was hyperglycemia. Right-sided lobectomy was performed, April 17. There was hyperglycemia. An incomplete left-sided lobectomy was performed, April 24. There was normal blood sugar at the beginning, but later it became high. The original weight was 10.8 kg.; April 24, the dog weighed 10.1 kg.; the weight, May 8, was 11.2 kg.

These three animals are alive and in excellent condition.

COMMENT

The glycosuria and hyperglycemia in diabetic dogs, after complete ligation of the thyroid vessels, or after complete thyroidectomy, provided tetany or infection does not occur, must be ascribed to the absence of thyroid hormones from the blood stream. When a condition of athyroidism established itself in the dog in Experiment 9, even repeated pancreatectomies did not cause the reappearance of glycosuria. The considerable gain in weight in this animal must also be credited to the condition of athyroidism created by the complete removal of the thyroid. The sugar tolerance in this animal remained high as in thyroidectomized dogs without diabetes. The dogs in Experiments 13, 14 and 15, in which a minute fragment of thyroid tissue was left at a second lobectomy, differed from the dog in Experiment 9 in that the glycemia remained high. The tendency to obesity, however, manifested itself in these animals, as in the dog in Experiment 9, which had been deprived of all its thyroid tissue.

Since the incompletely depancreatized dogs are still alive, one can only speculate as to the histologic picture in their remnants. But it is highly probable that a compensatory hypertrophy occurred in the fragment

Digitized by Google

left behind. Ribbert [25] was the first to point out that, in incompletely thyroidectomized dogs, hyperplasia occurs in the remnant, and this hyperplasia is usually noticeable in the peripheral acini. MacCallum [26] writes that the so-called typical hyperplastic type of exophthalmic goiter may be noted in dogs in the small fragment left after incomplete thyroidectomy. It is well known that in man hypothyroidism may go hand in hand with hyperthyroidism. A similar condition might have occurred as a result of incomplete removal of the thyroid in the dogs in Experiments 13, 14 and 15. On account of deprivation of the greater parts of their thyroids, a tendency to obesity was established.

For the persistence of hyperglycemia, of course, a compensatory hypertrophy might have been responsible. This would be quite in accord with clinical facts that the dextrose tolerance is low in hyperthyroidism and that there may be in man a combination of subthyroidism and glycosuria. It should be emphasized that the condition created in the three animals by partial pancreatectomy and incomplete thyroidectomy greatly resembles the preglycosuric or prediabetic state in man, i. e., increase in body weight and hyperglycemia.

The persistence of glycosuria after thyroidectomy, or after complete ligation of the thyroid arteries, when tetany develops, indicates the antagonism between the parathyroids and the thyroid. The high dextrose tolerance in nondiabetic thyroidectomized dogs in which the parathyroids were preserved has already been referred to.

TENTATIVE CONCLUSIONS

The question arises whether our experimental results can be applied to the treatment of human diabetes. Our material is not sufficiently large to permit definite conclusions. But the following line of reasoning leads

25. Ribbert: Ueber die Regeneration des Schilddrüsengewebes, Virchows Arch. f. path. Anat. **117**: 151, 1889.
26. MacCallum, W. G.: A Text Book of Pathology, Philadelphia, W. B. Saunders Company, 1916, p. 817.

Digitized by Google

one to believe that complete thyroidectomy in diabetics must be at least as effective. The advantages to man might be as follows:

1. The loss of the pancreatic islet, produced by complete or almost complete pancreatectomy, rarely has its counterpart in human diabetes.

2. The external apparatus in diabetes usually remains intact, so that even great losses in body weight resulting from this malady may be counteracted by thyroidectomy.

3. There is hardly a chance for a skilful surgeon to damage the parathyroids in man on account of the difference in the topographic relation of the latter to the thyroid.

4. Shock from the operation may be avoided by performance of the operation in two sittings.

One may hesitate in proposing complete thyroidectomy for the treatment of diabetes, since it has never been recommended, but one of Rohdenburg's [27] cases offers direct support for such a suggestion. The patient developed exophthalmic goiter during a course of diabetes mellitus. A part of the thyroid was removed. The glycosuria ceased and the patient remained sugar free for several years. In a second case of Rohdenburg, partial thyroidectomy was performed by Dr. Semken for exophthalmic goiter. Several years later glycosuria developed. Dr. Semken removed more of the thyroid, leaving only the isthmus. A complete cure occurred also in this patient.

It is perhaps worth mentioning that total removal of the spleen brings about a cure in hemolytic jaundice, the etiology of which is just as unknown as in diabetes mellitus. Although the majority of physicians believe that the chief trouble in the former condition lies in the spleen, others, for example, Pick and Strauss,[28]

27. Rohdenburg, G. L.: Thyroid Diabetes, Endocrinology 4: 63 (Jan.-March) 1920.

28. Pick, E., and Strauss, H., quoted by Hans Hirschfield: Erkrankungen der Milz, Berlin, Julius Springer, 1920, p. 232.

Digitized by Google

adhere to the hepatic origin of this malady. It is possible that a cure is accomplished in hemolytic jaundice because of removal of the gland which plays a secondary rôle in the disease. It is probable, then, that diabetes mellitus may be cured by removal of the gland which plays a secondary rôle in this malady. If the view that we take is correct, then complete thyroidectomy in two stages should be beneficial in diabetes mellitus of young children, in whom the mortality is about 100 per cent. The procedure may also be tried in diabetic adults who do not respond to any of the modern methods of treatment.

INTERPRETATION OF TABLES

Table 1: These dogs were starved from eighteen to twenty-four hours before blood was taken for estimation of glucose. The highest figures were obtained during the hot days of July.

TABLE 1.—BLOOD SUGAR IN NORMAL DOGS

No.	Mg. Sugar per Hundred C.c. Blood	No.	Mg. Sugar per Hundred C.c. Blood
1	53	8	90
2	83	9	78
3	56	10	98
4	76	11	104
5	78	12	104
6	67	13	104
7	94	14	100

Table 2: Nine males and six females whose body weights ranged from 6.7 to 20 kg., became persistently glycosuric after pancreatectomy. One dog became glycosuric after the removal of 1.3 gm. per kilogram of body weight. Dog 28, not included in this table, persistently showed glycosuria after removal of 1 gm. per kilogram of body weight. Dog 13, which was glycosuric, did not show an increase in the blood sugar content. The higher blood sugar figures in fourteen glycosuric dogs ranged between 290 and 125 mg. per hundred cubic centimeters of blood.

Digitized by Google

TABLE 2.—BLOOD SUGAR IN DOGS AFTER PANCREATECTOMY

No.	Sex*	Body Weight, Kg.	Weight of Removed Pancreas per Kilogram of Body Weight, Gm.	Weight of Removed Gland per Kilogram of Body Weight, Gm.	Sugar per Hundred C.c. Blood, Mg.	No. Days Following Operations When Sugar Determinations Were Taken
2	♀	10.0	23.0	2.30	208	3
3	♂	8.3	22.5	2.71	270	3
4	♂	7.5	18.2	2.42	250	3
5	♂	9.1	20.0	2.20	125	9
6	♀	8.7	21.0	2.42	298	6
7	♀	13.0	28.0	2.15	222	7
9	♂	6.7	17.0	2.53	200	7
15	♂	9.6	21.0	2.10	238	6
10	♀	20.0	44.0	2.20	238	6
13	♂	8.0	15.0	1.85	100	4
16	♀	13.8	20.0	1.45	228	5
17	♂	13.0	17.0	1.30	250	7
18	♂	17.8	35.0	1.96	200	7
14	♂	15.7	26.0	1.60	290	4
19	♀	12.0	23.0	1.90	228	4

* In this column, ♂ indicates male; ♀ indicates female.

TABLE 3.—BLOOD SUGAR IN NORMAL DOGS AFTER PARTIAL PANCREATECTOMY

No.	Sex	Body Weight, Kg.	Weight of Removed Pancreas per Kilogram of Body Weight, Gm.	Weight of Removed Gland per Kilogram of Body Weight, Gm.	Sugar per Hundred C.c. Blood, Mg.	No. Days Following Operations When Blood Sugar Determinations Were Taken
12	♂	11.2	27	2.70	127	5
14	♂	13.7	14	1.02	91	11
20	♂	22.0	13	0.60	108	5
					84	11
					133	18
		19.0	23.5	1.24	196	5
21	♂	17.7	18	1.02	79	5
		(second pancreatectomy)				
22	♂	27.2	22	0.80	143	11
23	♂	12.2	20.2	1.65	148	11
24	♂	9.0	14	1.55	158	10
25	♂	7.0	4.3	0.61	111	13
26	♂	10.5	11.9	1.10	143	9
27	♀	11.0	22.8	2.05	143	13

Digitized by Google

Table 3: Nine males and one female did not become glycosuric after partial pancreatectomy. The body weight ranged between 7 and 27.2 kg. Eight of ten became hyperglycemic. In one dog (Dog 20), vicarious hyperfunction of the pancreatic islets established itself eleven days after removal of the pancreatic tail, but the normal glycemia did not last. There was a greater increase in the glucose of the blood five days

TABLE 4.—BLOOD SUGAR IN GLYCOSURIC DOGS

	Mg. Sugar per Hundred C.c. of Blood				
No.	After Total Ligation	After Partial Ligation	After Thyroid-ectomy	Dates	Comment
4	192	...	...	Mar 7	Animal remained sugar free ten days after ligation
	90	...	...	Mar. 10	
	50	...	...	Mar. 14	
6	180	...	...	Mar. 25	Blood sugar diminished after ligation; increased with tetany
	240	...	...	Mar. 30	
9	...	214	...	April 17	Glycemia increased after partial ligation
15	200	...	...	July 1	Remained sugar free for fourteen days
	172	...	...	July 5	
10	213	...	...	July 14	Sugar free one day after ligation; reappearance of glycosuria with tetany
28	...	...	95	Feb. 15	Persistent glycosuria after partial ligation; sugar free 108 days after thyroidectomy
			86	Mar. 9	
			66	April 15	
17	...	285	...	Nov. 30	Increased blood sugar after partial ligation; sugar free on days when tetany free
			145	Dec. 2	
18	...	310	...	Dec. 10	Increased blood sugar after partial ligation; sugar free on days when tetany was absent
			238	Dec. 17	
			100	Dec. 22	

after the second pancreatectomy. Dog 12 did not become glycosuric, although 2.7 gm. of the pancreas per kilogram of body weight was removed.

Table 4: In these glycosuric dogs, the sugar from the urine disappeared after complete ligation of the thyroid vessels and after complete thyroidectomy, which was preceded by partial ligation when tetany did not occur. Partial ligation alone did not check the glycosuria. In Dog 28, the glycemia remained normal

Digitized by Google

for two months, and the sugar tolerance was normal after thyroidectomy. The blood sugar also became normal in Dog 4 and, in Dog 18 it became normal when tetany was checked by calcium lactate injections. Partial ligation of the vessels did not have any influence on the glycemia.

TABLE 5.—BLOOD SUGAR IN HYPERGLYCEMIC DOGS

	Mg. Sugar per Hundred C.c. of Blood				
No.	After One-sided Lobectomy	After Incomplete Removal of Second Lobe	After Complete Removal of Both Lobes	Dates	Comment
20	167	...	...	Mar. 4	Animal died from tetany four days after removal of second lobe
	181	...	...	Mar. 13	
23	...	...	102	Mar. 20	Blood sugar, in absence of tetany, normal; tetany prevented three days by calcium lactate injections
			100	Mar. 21	
			98	Mar. 22	
24	130	...	...	Mar. 28	Blood sugar became normal on April 12, but the glycemia remained high; great gain in weight
	152	...	...	April 1	
		143	...	April 2	
		185	...	April 4	
		100	...	April 12	
		137	...	April 24	
		123	...	May 2	
25	111	...	...	April 23	Drop in blood sugar to normal three days after lobectomy; glycemia remained high; gain in weight
		100	...	April 26	
		120	...	May 3	
26	105	...	...	April 24	Glycemia decreased at first, but become high; gain in weight
		100	...	April 27	
		124	...	May 3	
27	160	...	...	April 29	Blood sugar increased after removal of right lobe; animal died from tetany after removal of left lobe

Table 5: The blood sugar became normal in one of the hyperglycemic dogs (Dog 23) after complete thyroidectomy, and when tetany was kept in check by calcium lactate injections. The blood sugar in none of the dogs became normal after right-sided lobectomy. Dogs 24, 25 and 26 remained hyperglycemic after incomplete removal of the left lobe, although at first there was a drop of the blood sugar to normal. These dogs showed a tendency to obesity.

Digitized by Google

SUMMARY

1. Diabetes mellitus is primarily a disease of the insular apparatus of the pancreas, with an actual pathologic condition in severe cases.

2. The low sugar tolerance in all cases of hyperthyroidism suggests that the islands of Langerhans in this disease are always functionally affected, and that, occasionally, histologic changes in them may occur in those rare cases in which exophthalmic goiter and diabetes mellitus are combined.

3. Since overactivity of the thyroid caused by pathologic alteration in the gland upsets the pancreatic islets, a pathologic condition of the latter may functionally affect the thyroid.

4. The fact that true myxedematous individuals are not liable to become diabetic, and that a spontaneous cure from diabetes mellitus may occur through hypoplasia of the thyroid, brought about by various unknown causes, is highly suggestive that complete removal of the thyroid in man might have a curative effect for the malady.

5. That the removal must be a complete one becomes evident from clinical observations that subthyroidism and diabetes are found combined in the same individual.

6. The association of hyperglycemia with a tendency to obesity, in depancreatized nonglycosuric dogs after incomplete pancreatectomy, resembles the prediabetic state in man, i. e., hyperglycemia and increase in body weight.

7. Depancreatized glycosuric dogs become sugar free after complete ligation of the thyroid arteries or after thyroidectomy, preceded by partial ligation of the vessels, provided tetany or infection does not occur.

8. Partial ligation of the thyroid vessels or one-sided lobectomy has no effect in checking the glycosuria or the hyperglycemia.

Digitized by Google

9. From some considerations given in this discussion, it is probable that thyroidectomy in two sittings may be even more effective in human diabetes than in depancreatized dogs.

10. It is therefore suggested that complete thyroidectomy should be tried in the diabetes of children and in severe diabetes of adults who do not respond to the modern treatment.

63 East Eighty-Fourth Street.

ABSTRACT OF DISCUSSION

DR. WALTER M. BOOTHBY, Rochester, Minn.: An increase in carbohydrate tolerance is obtained by reducing the basal metabolism in patients with severe diabetes. This may be accomplished readily, as pointed out by Wilder, Boothby and Beeler, by an appropriate reduction in the total calories ingested and by keeping the protein intake low. A reduction in the basal metabolism can also be obtained by removal of the thyroid gland, but with many secondary disadvantages. The reduction in the basal metabolism and also the total metabolism probably explains the results obtained by Friedman and Gottesman. However, to infer that thyroidectomy is a desirable method of decreasing the basal metabolism, and thereby possibly increasing the sugar tolerance in diabetes is, I think, not the intent of the paper.

DR. CHARLES W. GREENE, Columbia, Mo.: It seems rather apropos of this paper, since Dr. Boothby did not mention this fact, to state that, in the first week of this month in Washington, Dr. J. J. R. Macleod reported an investigation in his laboratory in which they are isolating and testing the internal secretion of the pancreas. In diabetes experimentally produced they are able actually to get a deposit of glycogen in the liver if the amount of sugar in the blood is augmented by injection at the time of injecting the internal secretion of the pancreas. That fact has never been demonstrated before. It would seem that the Toronto laboratory is producing an extract of pancreas in which an internal secretion is prepared in sufficiently pure form for experimental purposes. At the time of the announcement, the encouraging promise was extended of a preparation pure enough for therapeutic purposes, applicable to the rather hopeless cases of pancreatic diabetes.

DR. ARNO B. LUCKHARDT, Chicago: If I understood Dr. Boothby correctly, he inferred that animals which had suffered partial or complete thyroidectomy were extremely sluggish. Dr. Dragstedt and I have animals alive months after complete thyroparathyroidectomy. These animals are

Digitized by Google

extremely active. No amount of thyroid feeding has changed them in the slightest degree. The question of the importance of the thyroid to the dog is interesting; one cannot produce symptoms of myxedema in the dog. You can remove both lobes and all four parathyroids without changing the animal in the least degree.

DR. A. J. CARLSON, Chicago: It is difficult to predict what will happen to the blood sugar in a dog on which a partial pancreatectomy has been performed. Even though we try to remove enough of the organ to produce the Sandmeyer type of diabetes, we cannot predict whether the dog will be partially diabetic for one, two or three weeks and then spontaneously recover and be perfectly normal so far as sugar tolerance is concerned, or whether he will gradually go down. The authors use the term pancreatectomy a little too loosely. While they give a number of experiments, I am not sure that the hyperglycemia they described has anything to do with the operation of the thyroid. I do not deny, of course, the fact that occasionally glycosuria and real diabetes are associated with toxic goiter, but, by the law of chance, we are going to have these together in one person, particularly in races having a higher percentage of toxic goiter as well as of diabetes. If the pancreatic diabetes is causally connected with thyroid hyperactivity or hypoactivity, that fact would have been brought out by the clinical condition more clearly than it is at present. I should like to emphasize the point that Dr. Luckhardt has brought out, that the story of thyroid function is by no means clear in all animals. Years ago, I fed from 10 to 20 gm. a day of desiccated (therapeutic) thyroid to dogs, without loss of body weight. We did not follow the basal metabolic rate, but one of the workers in our laboratory is following that at present and so far as this work goes, feeding dried thyroid to dogs, in ten times the therapeutic dose given to man, has not influenced the basal metabolic rate.

DR. G. A. FRIEDMAN, New York: I think it would be worth while to study the basal metabolism in depancreatized and thyroidectomized dogs. It is rather difficult to answer the question as to what the metabolic rate would be in such animals. However, the actual metabolic changes in them, from a practical standpoint, are unimportant. Our aim was to show the disappearance of glycosuria in depancreatized dogs after complete thyroidectomy or complete ligation of the thyroid vessels, when tetany did not occur. It was possible to free a dog from glycosuria after thyroidectomy. The animal gained considerably in weight and was lively, being on a liberal diet throughout. It is our impression that depancreatized and thyroidectomized dogs do not show signs of myxedema as compared with the stuporous condition of thyroidectomized nondiabetic dogs, which was noted by one of

Digitized by Google

us in experiments performed some years ago. The thyroidectomized normal animals are not so liable to develop tetany as diabetic dogs. Pancreatic extracts, but not the actual insular products, were administered intravenously to diabetic dogs by Meltzer and Kleiner. They showed that glycosuria was checked as long as injections were given. It is possible that the recently discovered endocrine product from the pancreas will have a transitory effect in diabetics similar to that of epinephrin in Addison's disease. One may succeed in raising blood pressure through injections of the drug for a short time, but one cannot obtain permanent results. In regard to Dr. Carlson's remark, our paper was practically an abstract and he will find more convincing evidence in the original. There is some evidence in the literature that the histologic picture in depancreatized dogs corresponds to the picture in overactivity. Our own histologic studies of the thyroids in depancreatized dogs we reserved for another paper. I believe it is of equal importance to investigate the iodin content of the thyroids in diabetic dogs. Such work is already in progress.

Digitized by Google

PNEUMOCOCCUS ANTIBODY SOLUTIONS SPECIFIC AGAINST TYPES I, II AND III *

F. M. HUNTOON, M.D.
GLENOLDEN, PA.

In the employment of immune animal serums as therapeutic agents, the curative effect resides in the antibody content, which is, in fact, an infinitesimal portion of the total amount of material present, so that, to obtain this antibody effect, a large amount of other substances must be administered, useless or even producing dangerous reactions.

Concentration methods based on salting out procedures can change the proportions, increasing the relative amount of the antibody to serum proteins, but cannot totally eliminate the latter. A method which to all practical purposes eliminates all the serum constituents with the exception of the antibody content marks a long step in the improvement of the products used in the biologic treatment of disease.

The pneumococcus antibody solutions, here described, are water-clear solutions containing antibody in approximately the same proportion as serum, but containing only a trace of horse serum, detectable by biologic but not by chemical means, a small amount of bacterial proteins, 0.85 per cent. sodium chlorid and 0.25 per cent. sodium bicarbonate.

In 1902, Landsteiner [1] demonstrated the possibility of separating normal hemagglutinin from its attachment to red cells, and that such recovered antibody retained its activities. Various observers [2] have since

* From the Mulford Laboratories.
1. Landsteiner: München. med. Wchnschr. 49:1905, 1902.
2. Huntoon, F. M.: J. Immunol. 6: 117 (March) 1921.

Digitized by Google

investigated this reaction, employing different antigen antibody combinations, but no attempt had been made to employ this dissociated antibody therapeutically. Gay and Chickering,[3] in 1915, utilized the observed fact that the precipitate formed during the precipitinogen-precipitin reaction carried down with it other antibodies present, to purify antipneumococcic serum, and employed such solutions to treat a few cases of pneumonia.

However, since such a precipitate is in great part derived from the serum proteins, their solutions contained serum and gave serum reactions. In the preparation of our antibody solutions, we have avoided this reaction and have used only formed and ponderable antigens, which could be washed free of serum.

The method of preparation of our solutions is as follows: Pneumococci of the three fixed types are exposed to the action of a large amount of an antipneumococcic immune serum, multivalent for Types I, II and III. The sensitized organisms are removed by centrifugation, carrying the attached antibody with them. The bacteria are then washed free of serum by repeated changes of salt solution. Finally, they are emulsified in salt solution containing 0.25 per cent. sodium bicarbonate, and are heated to 55 C. for from thirty minutes to one hour. The emulsion is again centrifuged, and the supernatant removed, chilled, recentrifuged, and finally filtered through a filter candle.

The experimental work bearing on this question of the recovery of attached antibody has been published elsewhere,[4] together with evidence bearing on the nature of antibody. The object of the investigation was from the start to determine the possibility of the production of serum-free solutions containing sufficient antibody to permit of their use therapeutically in the treatment of lobar pneumonia.

3. Gay and Chickering: J. Exper. Med. **21**: 389, 1915.
4. Huntoon, F. M., and Etris, E.: J. Immunol. **6**: 123 (March) 1921.

Digitized by Google

When the methods were sufficiently perfected to produce fairly large amounts of the multivalent antibody solutions, the sterile solutions were prepared in 50 c.c. vials for intravenous administration, and arrangements were made for the actual clinical testing of the material.

This clinical experiment extended through the winters of 1920-1921 and 1921-1922, and at this time more than 600 cases of pneumonia have been treated. This portion of the work was conducted by Dr. Lewis A. Conner [5] at the New York Hospital and by Dr. Russell L. Cecil and Dr. Paul Larsen [6] at the Bellevue Hospital, New York.

In such an experiment, the interpretation of the figures obtained is difficult; but when the cases are followed carefully, it is possible to decide on the therapeutic efficacy of certain treatments.

In Dr. Conner's series of 114 cases of pneumonia, including pneumococcus pneumonias and those caused by other organisms, the total mortality was 14.6 per cent., which is 8 per cent. below the lowest previous mortality in the history of the hospital and 16 per cent. below the usual rate. In pneumococcus pneumonias, the rate was 10.6 per cent. In Dr. Cecil's series of 1,000 cases, studied bacteriologically and clinically, in which half were untreated controls, the mortality in all cases was reduced approximately 7 per cent. over the controls.

The details of these reports cannot be gone into in this paper except as the clinical effect indicates the nature of these antibody solutions and their action on the human system and on the causative organisms.

The chemical constitution of the solutions and the antibody content against the three fixed types which led to the determination that such solutions would be

5. Conner: Read before Association of American Physicians, Washington, May 3, 1922.

6. Cecil, R. L., and Larsen, N. P.: Clinical and Bacteriologic Study of One Thousand Cases of Lobar Pneumonia, J. A. M. A. 79: 343 (July 29) 1922.

Digitized by Google

useful as a therapeutic agent is shown in the following outline and the accompanying table.

Pneumococcus antibody solution.
  Antibody content—0.2 c.c. protects mice against 1,000,000 fatal doses of Type I pneumococcus.

Chemical analysis for protein content:
  Total nitrogen—0.035 mg. per cubic centimeter.
  Nitrogen in phosphotungstic acid precipitate—0.028 mg. per cubic centimeter.
  Monoanimo acids—none.

Chemical reactions.
  Color reactions.
    Biuret—negative.
    Xanthoproteic—negative.
    Adamkiewicz—negative.
    Ehrlich's (dimethylaminobenzaldehyd)—negative.
    Millions—negative.
    Ninhydrin—negative.
  Sulphur—negative.
  Phosphorus—negative.

An examination of the outline and the table will show that there was a very considerable antibody content, and that the serum proteins had been eliminated as far as chemical reactions could detect them.

However, a routine testing on guinea-pigs made for toxicity revealed a sensitizing effect. Doses of 5 c.c. would sensitize a certain proportion of pigs to a subsequent injection of horse serum. A summary of this experiment is presented in the following outline:

Sensitization of guinea-pigs to horse serum by antibody solutions.
    Dose, Antibody, 5 c.c.; route, Intraperitoneal.
  Incubation period, fifteen days.
  Test dose, 1 c.c. horse serum; route, intravenous.
  Number of solutions tested, 28.
  Number of guinea-pigs employed, 44.
  Number of Guinea-pigs dying of anaphylactic shock, 13.
  Guinea-pigs showing possible symptoms of anaphylaxis, 13.
  Guinea-pigs showing no symptoms of anaphylaxis, 18.

Controls:
  Three guinea-pigs received 5 c.c. of horse serum diluted 1:50,000, by the intraperitoneal route.
  After fifteen days, injected intravenously with 1 c.c. horse serum.
  All three died of anaphylactic shock.

Digitized by Google

This experiment showed that, although no serum proteins were found by chemical means, they were still present in a very small amount, detectable only by means of the biologic test.

On the practical side, however, none of 600 treated human cases have shown symptoms of anaphylactic shock or of serum sickness, although the antibody solutions have been given to those so sensitive to horse serum that serum itself could not be used, and to those who had received injections of horse serum at some previous time.

PNEUMOCOCCUS ANTIBODY SOLUTION: CONTENT OF ANTIBODY AGAINST TYPES I, II, III PNEUMOCOCCUS

Dose Antibody, C.c.	Culture Type I, C.c.	Mice	
0.2	0.01	Lived	Lived
0.2	0.04	Lived	Died 40 hours
0.2	0.1	Lived	Died 19 hours
Virulence:			
	0.000,000,001	Died 40 hours	Died 40 hours
	0.000,000,01	Died 25 hours	Died 40 hours
Dose Antibody, C.c.	**Culture Type II, C.c.**	**Mice**	
0.2	0.001	Lived	Lived
0.2	0.01	Lived	Lived
0.2	0.1	Lived	Lived
Virulence:			
	0.000,000,01	Died 44 hours	Died 27 hours
	0.000,000,1	Died 44 hours	Died 27 hours
Dose Antibody, C.c.	**Culture Type III, C.c.**	**Mice**	
0.2	0.001	Lived	Lived
0.2	0.01	Lived	Lived
0.2	0.1	Died 27 hours	Died 19 hours
Virulence:			
	0.000,000,01	Died 64 hours	Died 40 hours
	0.000,000,1	Died 27 hours	Died 23 hours

The intravenous use of these solutions is usually accompanied by a reaction simulating that sometimes seen on the intravenous injection of therapeutic serums. From twenty to thirty minutes after the injections, the patient has a chill, followed by a rapid rise of temperature to sometimes alarming heights. This persists only a short time and is followed by profuse sweating.

The patient is very uncomfortable at the height of the reaction, but with the subsequent fall in tempera-

Digitized by Google

ture, often to normal, the pulse and respiration rate also falls to below the previous rate, and there is a distinct betterment in the appearance and feelings of the patient.

The source of this reaction has been the cause of much speculation, and it is not at this time settled. It did not appear in any of the few cases treated subcutaneously. This reaction may be due to the bacterial protein present, to the rapid destruction of bacteria in the body, to the so-called salt fever or to some cause as yet unsuspected.

The relation of the shock to the therapeutic effect is also undecided; but, in the series of cases in which the pneumonia was caused by *Streptococcus hemolyticus,* the injections of antibody caused similar reactions without any beneficial effect on the death rate. It is also interesting in this connection to note that straight pneumococcus infections showed more improvement in the death rate than when mixed infections were present.

It can be fairly said that the results with this material are promising, in that there is a distinct reduction in the death rate from lobar pneumonia, but that this treatment should not be used promiscuously but should be employed with judgment. The severe reaction encountered in many cases limits its usefulness in the old, in exhausted cases late in the disease and in those with a conincident heart affection. It is hoped that further experience will enable this class of cases to be treated by these solutions, perhaps by the subcutaneous route.

In vigorous cases, particularly in the first three days of the disease, one may expect a certain number which will promptly defervese after one or two doses, the disease being cut short.

The production of these solutions in which antibody exists relatively free from associated serum proteins has enabled us to attack the problem of the nature of

Digitized by Google

antibodies with more freedom than when they are present in the colloidal mixture called serum, and many results of interest have been obtained.

It can be stated with considerable certainty that antibody is soluble in distilled water, in salt solution, in weak acids or weak alkalis. It is not easily affected by trypsin in these solutions, although when present in serum they seem to be rapidly destroyed or inactivated by this enzyme. Antibody solutions keep perfectly under conditions that cause immune serums to deteriorate, exposure to incubator temperature of 38 C.

The three cresols, phenol (carbolic acid) and liquor formaldehydi, when added in amounts usual in preserving serum, affect the potency of the antibody solutions, owing probably to the lack of protein material to protect the antibody. This necessitates the use of sterile antibody solutions without preservative. The heating of the antibody solution causes the inactivation of the antibody at the same temperatures which have been noted in the many tests on immune serums. Under proper conditions, antibody solutions may be dried and the antibody content recovered in toto.

Recently, two interesting observations have been made: 1. Sensitized bacteria may be digested for seventy-two hours in absolute alcohol, if the alcohol is now removed, antibody may still be split off from the bacteria with little loss. If the alcohol employed is evaporated to dryness and the residue taken up in salt solution, a small amount of antibody will be found present. This shows that antibody, as such, is neither destroyed nor coagulated by absolute alcohol, a point to be borne in mind in discussing the possible protein nature of this substance.[2] On the addition of ammonium sulphate to these solutions, although some slight precipitate may occur of the bacterial proteins present, even after progressive additions with prolonged centrifugation and filtration through hardened filter paper between the additions some antibody will

Digitized by Google

remain in solution, even after 80 per cent. saturation. The antibody does not follow the laws for the precipitation of either englobulin or pseudoglobulin.

If we consider the known facts about this substance, the theory of its globulin nature is rendered untenable. Whether it belongs among the albumins cannot now be stated. It may possibly be a racemized protein or belong with those proteins whose molecule is just too large to pass the dialysing membrane.

That antibody is not a dialysable substance has long been known and other observers and we ourselves have assumed for this reason that it might be a large molecule substance. A recent reconsideration of this subject has led me to doubt the validity of this assumption. It is doubtful whether anyone has obtained antibody in what may be called a free unattached state. Its ready absorption by many substances, its propensity to be precipitated from serums with certain fractions, its removal by the precipitin-precipitinogen precipitate, its readiness to be partially removed from our solutions by precipitates caused either by dialysis or salting out methods render it probable that, whether in serum or in serum-free solutions, it is always more or less closely associated with some protein molecule.

In the case of our solutions, it would be found associated with a bacterial protein, and certain observations on the filterability of these solutions and the influence of alkalis on this process have led us to the conclusion that this is so, and that this bacterial protein is in all probability what is termed antigen.

This association would account for the failure of antibody to be dialysed and is not incompatible with the activities of the solution, since Morgenroth [7] has shown that sensitized red cells give up part of their antibody charge to unsensitized red cells; and we have demonstrated the same reaction with bacterial agglutinins in the test tube, and with the pneumococcus protective antibody in vivo.

7. Morgenroth: München. med. Wchnschr. **50**: 61, 1903.

Digitized by Google

Opposed to this point of view is the fact that antibody is present in serums and in our solutions in extremely small chemical amounts, and must be highly dispersed. The rapid action of antibody under certain conditions hardly permits of the conception that it is attached to molecules of the size of the highly organized serum proteins. It is interesting to note in this connection the influence of inorganic salts on the removal of antibody from sensitized bacteria.

Sodium chlorid prevents in a measure the splitting off of agglutinins but has no effect on the pneumococcus protective antibody. This latter substance, however, is influenced by calcium phosphate, not being released to any extent in its presence but coming off readily in its absence. These observations might lead to a conception of a binding salt which entered into the antigen antibody relation and which, when removed by persistent washing (progressive dilution), allowed the combination to break up or as suggested above, allowed the proteins of the bacteria in union with the antibody to split off from the mother cell.

This again leads to the deduction that the portion of the bacterial cell in combination with an agglutinin differs chemically from that portion in combination with the protective antibody. If it becomes possible to separate agglutinins from the protective antibody, which from some of our experiments would seem probable, we may be able to obtain more information about the essential characteristics of antigen, which is as yet territory as little explored as that of antibody.

Although the scientific side of this problem is and must be for a long time in an uncertain state, the utilization of the phenomena now known enables the production of antibody solutions which are relatively pure, in sufficient concentration to be available for therapeutic purposes; and the way is opened for experimental research leading to the determination of the nature of both antibody and antigen.

Digitized by Google

Since the determination of the therapeutic value of such material depends entirely on the clinical test, it must be emphasized that such careful and painstaking clinical observation as has been undertaken by Dr. Conner and Dr. Cecil cannot be too highly praised. This extensive and laborious therapeutic experiment could only be made possible by the cordial cooperation of all of the various institutions interested and the scientific enthusiasm of the staffs concerned.

ABSTRACT OF DISCUSSION

DR. JOHN A. KOLMER, Philadelphia: This is a subject of primary importance not only in relation to the chemical nature of antibodies from the academic standpoint, but also in relation to serum therapy and anaphylaxis. The chemical nature of antibodies has attracted the attention of many investigators, and up to the present time the consensus of opinion has been that what we call antibody is closely associated with the globulin fractions of immune serum; but I think it has been brought out very clearly that the exact nature of antibody is as yet unknown. I hope that Dr. Huntoon will continue his chemical studies with the idea of throwing more light on this subject. Since his antibody solution does not sensitize individuals to horse proteins, it will have a very valuable application in the serum treatment of disease, providing the general nonspecific reactions are not too severe. I gathered from Dr. Huntoon's paper that his experiments have been conducted with antipneumococcic serum. Have similar "antibody solutions" been prepared with other immune serums?

DR. JOHN A. MURPHY, Swarthmore, Pa.: The clinical use of the pneumococcus antibody solution in the treatment of pneumonia deserves serious thought. The character of the large well controlled clinical experiment carried on in New York by Dr. Cecil and Dr. Larsen, comprising 1,000 cases of pneumonia, all types, about equally divided between treated and untreated cases, warrants such thought. None of the treated cases presented any symptoms of anaphylaxis, a feature which will commend the antibody solution to the profession and should assure it a place in therapeutics. The intravenous use of the antibody solution is usually followed by a thermal reaction characterized by a chill and a sharp rise in temperature, often three or four degrees above its registration at the time of injection. This reaction appears in from twenty to forty-five minutes, and is somewhat alarming in its manifestations, subsiding within thirty minutes, when the temperature rapidly falls to normal or lower, and

Digitized by Google

the clinical bed picture changes from the labored distress of the pneumonic patient to one of general comfort and well being. A general understanding, both of the expectancy and the nature of the reaction, together with the therapeutic results (reported in the section on medicine), should serve to broaden the therapeutic use of the antibody solution.

DR. FRANK M. HUNTOON, Swarthmore, Pa.: It is very easy to prepare typhoid agglutinin, meningococcus or streptococcus antibody, but the preparation of this material to be used therapeutically is a game of chance. Agglutinins as such are much harder to prepare than protective antibody, for various reasons. The use of distilled water in the preparation of agglutinin antibody tends to dissolve the cells to a much greater extent. With the meningococcus, you can get antibody solutions that show both opsonic and complement fixation; but the tendency of the meningococcus is to dissolve in salt solution. These solutions are likely to be opalescent, and as such would not be available therapeutically. The principle of the production of these solutions is very well established. Antibodies which show different effects are split off readily under somewhat different conditions, owing, perhaps, to combinations with different antigens. I do not want to seem too pessimistic about these solutions as therapeutic agents, but I do not believe that these solutions are going to be generally employed. They may become generally available, but they will not become generally used for the very reason that the accompanying reaction will disturb the physician. If a patient should die during the reaction, the blame will be placed on the physician. If the patient recovers, it will be said to be in spite of the reaction. A sufficient experience, however, will leave no doubt in the mind of the observer that these solutions exert a profound influence in many cases.

Digitized by Google

PRODUCTION OF ARTERIOSCLEROSIS IN RABBITS BY DIETS RICH IN ANIMAL PROTEINS *

L. H. NEWBURGH, M.D.
AND
SARAH CLARKSON, M.S.
ANN ARBOR, MICH.

In a note published two years ago, Newburgh and Squier [1] reported the occurrence of atherosclerosis in two small groups of rabbits, eleven in all, that had been fed high protein diets. While the evidence at hand indicated that the vascular lesion had been caused by the diets, such a conclusion was not safe because the experiments were too few to permit a generalization.

The present communication is an abstract [2] of the further investigation of the effect of high protein diets on the arteries of rabbits.

The term atherosclerosis, as used by most pathologists, is intended to designate a primary disease of the intima and to exclude lesions of the intima which result from disease of the media or vasa vasorum. The gross and histologic characteristics of this primary intimal disease are so well known to this group that further description is unnecessary.

Two series of animals have been fed the experimental diets. The first series received food containing 36 per cent. of protein, and the second series ate a diet containing 27 per cent. of protein. The diet yielding 36 per cent. of protein was made by mixing together equal parts by weight of dried, powdered lean beef

* From the Department of Internal Medicine, University of Michigan Medical School.

1. Newburgh, L. H., and Squier, T. L.: High Protein Diets and Arteriosclerosis in Rabbits, Arch. Int. Med. **26**: 38 (July) 1920.

2. A complete report of these studies will shortly be published.

Digitized by Google

(81 per cent. protein), wheat flour and bran, to which was added 1 per cent. of sodium chlorid and 5 per cent. of "baking powder," and enough water to make a stiff dough. The mass was baked in a hot oven for about one hour. The mixture containing 27 per cent. of protein was prepared in the same way except that one part of the powdered beef was mixed with two parts each of flour and bran.

In addition to this food, the rabbits were given about 100 gm. of greens one or twice a week.

Rabbits that had been raised outdoors under excellent conditions were selected. They were housed during the experiment singly or in small groups in unheated pens protected from rain and wind.

Twenty-four animals lived for four weeks or more on a diet containing 36 per cent. of protein. These twenty-four animals may be conveniently divided into three groups determined by the duration of the experiment. In the first group are ten animals that lived from four to eight weeks on the diet. Two of these showed very early intimal disease. Six rabbits lived on the diet from ten to sixteen weeks, and four of them showed early intimal disease. The remaining eight rabbits ate the high protein mixture from eighteen to thirty-six weeks, and all of them showed marked and extensive atherosclerosis.

Fifty-one animals were fed the diet containing 27 per cent. of protein. These rabbits fall naturally into two groups: forty that lived less than twenty-six weeks, and eleven that lived from twenty-six to fifty-nine weeks. None of the forty rabbits that lived for less than six months on the diet containing 27 per cent. of protein showed atherosclerosis of the aorta; whereas, eight of the eleven animals that lived on this diet for more than six months presented aortic lesions which were grossly and histologically typical of true atherosclerosis. The vascular lesions in seven of these eight rabbits were advanced and extensive. The eighth

Digitized by Google

rabbit that had eaten the diet for just six months showed an early but widely distributed process.

From this summary of results it is evident, first, that animals which ate a diet containing 36 per cent. of protein showed the atherosclerosis sooner than the rabbits that received only 27 per cent. of protein; and, secondly, that the occurrence and extent of the atherosclerosis is roughly proportional to the duration of the feeding.

These facts strongly suggest that the vascular lesions were produced by the diet; but before being certain that such is the case, it is necessary for us to investigate two sources of error. It is not inconceivable that rabbits which are confined in laboratories for many weeks or months may be exposed to some conditions which in themselves are capable of causing atherosclerosis. In order to answer this question, nineteen rabbits were set aside in a large pen and were cared for as ordinary stock animals, except that, when one of these nineteen rabbits came down with an infection, he was not removed but was, on the contrary, allowed to remain with his fellows until he eventually died. This was done in order to accentuate the unfavorable conditions of the laboratory and thus make the control more rigid. Twelve of these animals lived more than six months. Not a single example of atherosclerosis was found in these nineteen rabbits. Hence the vascular lesions seen in the animals that ate the high protein diets were not an outcome of mere residence in the laboratory.

A second possible source of error is in the question of how often spontaneous atherosclerosis occurs in rabbits. We have examined the aortas of 116 supposedly normal rabbits. Four of them or 3.5 per cent., showed small, wartlike lesions of the upper aorta. Steinbiss [3] found no arterial lesions in 500 normal

3. Steinbiss: Arch. f. path. Anat. **212**: 152, 1913.

Digitized by Google

rabbits, and Loeb [4] found only normal aortas in 483 control rabbits examined by him. Spontaneous vascular disease, accordingly, is a negligible source of error in our experiments.

Since neither the conditions prevailing in our laboratory nor the spontaneous occurrence of aortic lesions will account for the atherosclerosis in our experimental animals, we feel justified in asserting that this atherosclerosis was caused by the diet.

This lesion, as seen by the unaided eye, is made up of discrete and confluent, raised, opaque, white streaks and plaques. The process is always most marked in the upper thoracic aorta and, in early cases, may be limited to a few closely set, tiny plaques restricted to the arch. As the process becomes older and more marked, the individual lesions become larger and extend farther down the aorta. In advanced examples, one of which is shown in Figure 1, the plaques and streaks are thickly distributed along the whole aorta, and may even extend a few centimeters into the great vessels given off by the aorta. In the upper aorta, the fusion of the plaques often results in the entire disappearance of normal intima. Not infrequently, the lesion extends into the aortic valves, causing them to become thick and stiff. In a few instances, the mitral valve was similarly involved.

The lesion, when examined with the microscope, is clearly a primary disease of the intima. It begins with a necrosis or fatty degeneration of the endothelial cells. The initial injury is very quickly followed by great thickening of the intima, owing to the presence in it of large cells loaded with fat and embedded in a hyperplastic elastic tissue (Fig. 3). At a somewhat later stage, when repair is being attempted, the picture will have added to it a broad band of fibrous tissue on the lumen side of the lesion (Fig. 4). Below this is the area of degeneration, which may have by now

4. Loeb: Deutsch. med. Wchnschr. 39: 1819, 1913.

Digitized by Google

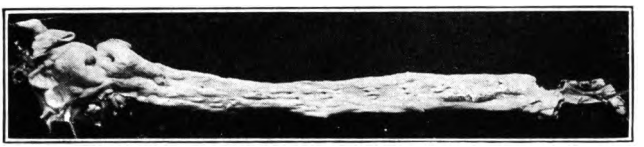


Fig. 1.—Aorta of rabbit given a diet containing 27 per cent. of protein for nine months; note the irregular plaques and streaks; the normal intima of the arch is entirely replaced by a broad confluent plaque.

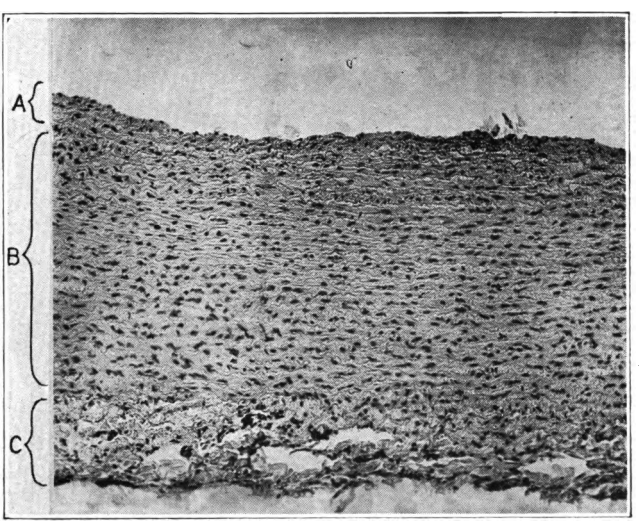


Fig. 2.—Normal aorta: *A*, the narrow intima; *B*, broad muscular media; *C*, adventitia.

Digitized by Google

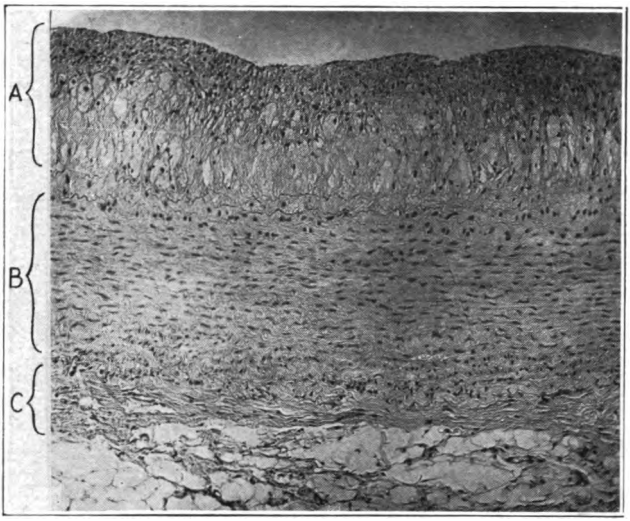


Fig. 3.—Aorta of rabbit in which atherosclerosis was moderately advanced; a diet containing 27 per cent. of protein was fed for nine months. *A*, great thickening of intima brought about by the large vacuolated cells and a hyperplastic elastic tissue; fat stains demonstrate that the vacuoles are filled with fat; *B*, normal media; *C*, adventitia.

Digitized by Google

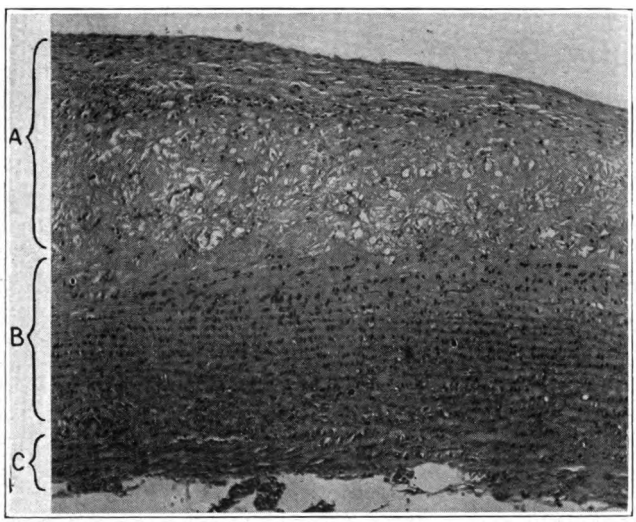


Fig. 4.—Aorta of rabbit in which atherosclerosis was far advanced; a diet containing 27 per cent. of protein was fed for eleven months. *A*, intima, showing a band of dense fibrous tissue on the lumen side of the vessel below this arc; degenerated, fat-containing cells; *B*, the degeneration has progressed far into the media; *C*, adventitia. Other sections of this aorta show masses of calcium scattered irregularly through the area of degeneration.

Digitized by Google

Digitized by Google

invaded the media to a variable degree and which will still show enormous amounts of fat.

Investigators have from time to time claimed to have discovered an etiologic agent of human atherosclerosis, on the ground that this agent had caused vascular injury in rabbits. Before such claims should be given any weight, their supporters should demonstrate that the experimental arterial lesion bears at least a very close resemblance to the disease in the human being.

More often than not, the vascular lesions obtained by students in this field have failed to suggest human atherosclerosis. Among the relatively few successful investigations, the work of Ignatowski[5] is of great importance. In summing up his results, he pointed out that all rabbits that were fed animal protein showed primary intimal disease of the aorta. The accompanying description of the lesion, although far from complete, was nevertheless sufficient to indicate that it bore a strong resemblance to human atherosclerosis. This work was soon followed by a number of investigations directed toward an analysis of the chemical mechanism which is responsible for the deleterious effect of animal diets on the arteries of rabbits.

Both the gross and the histologic pictures seen in the experimental aortic lesions resulting from our high protein diets, are so similar to corresponding stages of human atherosclerosis as to leave no doubt that the human type of primary intimal disease has been produced.

In spite of the close resemblance between our experimental atherosclerosis and the disease as it occurs in man, it is not claimed that the abuse of protein causes human atherosclerosis. The available experimental facts do not permit a final answer to this question. The vascular system of omnivorous man may have

5. Ignatowski: The Action of Animal Protein upon the Aorta and Parenchymatous Organs of Rabbits, Arch. f. path. Anat. **198**: 248, 1909.

Digitized by Google

acquired an insusceptibility to the products of protein metabolism, not possessed by the herbivorous rabbit. It may, on the other hand, be true that the arteries of man are as easily injured by the derivatives of protein as are those of the rabbit; or, finally, that man has acquired only a partial immunity which may be broken down by years of a protein intake two or three times greater than is needed to maintain health.

SUMMARY

Spontaneous atherosclerosis is a very rare disease in rabbits. Diets containing 27 and 36 per cent. of protein derived chiefly from beef have produced true atherosclerosis in the rabbit. The time of appearance and the extent of the lesion were roughly proportional to the amount of protein in the diet and the duration of the feeding.

We are grateful to Dr. A. S. Warthin and Dr. C. V. Weller for help in interpreting the histologic preparations, and for the photomicrography.

ABSTRACT OF DISCUSSION

DR. M. W. LYON, JR., South Bend, Ind.: I am glad that Dr. Newburgh was uncertain whether the lesion in rabbits could be exactly comparable to similar lesions in human beings on account of the zoologic difference between the subjects. I think anatomic and zoological investigations in human beings would establish the fact that men have had a rather high protein diet for many generations and have become accustomed to it; whereas, the rabbit is one of the most strictly herbivorous mammals known. It is even more strictly herbivorous than many of the true rodents. The real origin of rabbits is probably from some preungulate ancestor. It seems to me that it might be advisable to try the experiments on an animal which has a diet much more like that of human beings than the rabbit, such as the ordinary hog. The hog has probably been eating a protein diet for a long time. I think there are few hogs in the wild or the domestic state that will not eat much protein if they can get it. I doubt that we should conclude that we can produce arteriosclerosis in ourselves by a protein rich diet, despite these experiments which have been performed so carefully. I do not doubt that Dr. Newburgh does produce it in rabbits, but I think we should be cautious in applying his observation to man.

Digitized by Google

DR. L. H. NEWBURGH, Ann Arbor, Mich.: Dr. Fox of Philadelphia has examined all of the animals that have died in the Philadelphia Zoological Garden. His conclusions are of interest in this connection. He pointed out that the carnivora had chronic vascular and renal lesions, and that they were practically the only ones that had such lesions. I wrote to Dr. Fox, asking him whether I was justified in assuming that a definite relationship existed between the carnivorous diets and these chronic lesions of the arteries and kidneys. In his reply, he stated that this certainly was true, that the meat-eating animals showed a high incidence of chronic disease of the arteries and the kidneys as compared with all the other animals on which he had performed necropsies.

Digitized by Google

THE CONGENITAL FACTOR IN CHRONIC RENAL DISEASE

EDWARD WEISS, M.D.
Associate in Pathology, Jefferson Medical College.
PHILADELPHIA

The purpose of this report is to record briefly the clinical notes and pathologic findings in three uncommon cases of chronic renal disease occurring in comparatively young persons, associated with a marked degree of nitrogen retention and running a rapidly fatal course. In addition, because of the absence of a definite etiologic factor, together with an unusual appearance of the kidneys at necropsy, the importance of a congenital basis is emphasized, as an etiologic factor in these and similar cases.

REPORT OF CASES

CASE 1.[1]—J. M., a white man, aged 37, a policeman for the last fifteen years, who was admitted to the Jefferson Hospital in the service of Dr. H. A. Hare, April 12, 1921, complained of shortness of breath. His family history was negative. He had had typhoid fever at 13, gonorrhea at 22 and influenza at 33, from all of which he had apparently made a good recovery. For the last two or three years, he has had to get up once or twice at night to urinate, but otherwise he enjoyed good health until seven weeks prior to admission, when he was suddenly seized with dyspnea during the night, and this had continued.

The patient was fairly well nourished and had marked pallor. The area of cardiac dulness was somewhat increased to the left; the blood pressure on admission was 220 systolic and 180 diastolic; there was no edema. Urinalysis revealed a cloud of albumin and a few hyaline and granular casts. Hemoglobin was 56 per cent.; the Wassermann test of the blood and spinal fluid was negative. Eye ground examination disclosed a moderate albuminuric retinitis. The phenolsulphonephthalein test gave only traces of dye elimination in

1. Reported from the standpoint of nitrogen retention by Weiss Edward, and Garner, V. C.: J. Lab. Clin. Med. 7: 229 (Jan.) 1922.

Digitized by Google

two hours. The two hour test of urine indicated a fixation of specific gravity at about 1.011 and a total volume, in the twenty-four hours, of 1,080 c.c.

The general condition of the patient grew steadily worse; his nocturnal dyspnea increased in severity. April 19, seven days after admission, he became drowsy and developed a persistent diarrhea, which continued for three days before yielding to treatment. He vomited occasionally and, April 26, a pericardial friction rub was heard. May 1, there was a decided change for the worse, and death occurred, May 4.

Of greatest help from a prognostic standpoint were the estimations for nitrogen retention in the blood. An initial blood urea nitrogen of 93 mg. rapidly rose and, twelve hours before death, eighteen days later, reached 304 mg. The creatinin, 13 mg., and nonprotein nitrogen, 401 mg., paralleled this remarkable rise in the urea nitrogen.

The necropsy, performed on the day of death, revealed a marked chronic interstitial nephritis, arterial disease, and left-sided cardiac hypertrophy, with an ulcerative colitis and serofibrinous pericarditis.

The kidneys weighed only 80 gm. each, and did not present quite the usual picture of marked chronic nephritis, in that they were not so coarsely granular; advanced scarring was not a feature, and there was no increase of pelvic fat; in other words, the kidneys seemed naturally small, rather than atrophic. The microscopic picture was that of a marked chronic interstitial nephritis with great fibrous tissue increase, thickened capsule, shrunken and fibrosed glomerular tufts, periglomerular small cell infiltration, atrophy and dilatation of tubules, the formation of retention cysts, and sclerosis of the blood vessels.

Summary: A congenital basis for this case of renal disease is suggested by the absence of a definite etiologic factor in the history and physical examination of this comparatively young man, who had shown a rapidly progressive loss of renal functional power, an enormous nitrogen retention and death from asthenic uremia; with the findings at necropsy of kidneys which appeared hypogenetic rather than atrophic, and with but slight sclerosis of the systemic bloodvessels.

Case 2.—S. K., a white man, aged 26 years, who was first admitted to the tuberculosis wards of the Philadelphia General Hospital, Nov. 16, 1921, gave a history of a dry, hacking cough of five or six years' duration; pain in the chest; blood-tinged sputum in the last month or two, and a loss of 40 pounds (18 kg.) in weight in the last four months. A good history could not be obtained, as the patient was a foreigner and spoke English with difficulty; but later the further facts were elicited that about five months previously he began having severe frontal headaches, epigastric discomfort and vomiting after meals, and edema of the face and ankles. For the last three or four years, he had had nocturia.

Digitized by Google

He was transferred to the medical wards, in the service of Dr. Riesman, November 23.

The family history of the patient was unimportant except that his father died at 56 of "kidney trouble." His own history disclosed nothing important; he did not recall the diseases of childhood, and denied venereal disease and the use of alcohol. He had a slight attack of influenza in 1918.

The patient was fairly well nourished; there was slight edema of the face. The heart was slightly enlarged; the peripheral vessels were soft; the pulse was 90; the systolic blood pressure was 180; the diastolic, 135.

Urinalysis revealed a specific gravity of 1.010, a cloud of albumin, and occasional granular casts. The patient failed to eliminate any of the dye in two hours in the phenolsulphonephthalein test. Examination of the eye grounds disclosed an albuminuric retinitis with hemorrhages.

November 23, a pericardial friction was heard, and this persisted until December 5, about which time the the patient became stuporous, and died, December 15.

November 22, the blood urea nitrogen was 126 mg., and creatinin 7 mg. Both abruptly rose, and the day before the death of the patient, twenty-two days later, had reached tremendous figures: 327 mg. of blood urea and 20 mg. of creatinin.

Necropsy, the following day, revealed an advanced chronic interstitial nephritis; hypertrophy of the heart; hydroperitoneum and bilateral hydrothorax; hemorrhagic pericarditis, and a slight degree of atheroma of the aorta.

The kidneys were small, the left weighing 115 gm., the right, 95 gm., and fairly firm, but the capsules stripped easily and left finely granular surfaces. The incised surfaces were pale; the cortices were only slightly narrowed, and the pelvic fat had not increased in amount.

The microscopic picture was that of a well advanced chronic interstitial nephritis with a superimposed acute tubular lesion.

Summary: This rapidly fatal chronic nephritis in a young man, associated with very marked nitrogen retention, the absence of a definite etiologic factor and, again, the appearance at necropsy of kidneys which seemed naturally small rather than shrunken, suggests in this case even more strongly than in the former one, because of the younger age, a congenital basis. The microscopic finding of a superimposed acute tubular lesion suggests that this was the determining cause of death and that, up to the time at which this lesion occurred, the kidneys were sufficient for ordinary demands, breaking down under the strain of an acute lesion probably brought about by a slight cause—an otherwise negligible infection.

Case 3.—M. H., a white girl, aged 15, who was admitted to Jefferson Hospital in the service of Dr. Loux, Dec. 13, 1921, complained of pain in the left side of the back, weakness and

Digitized by Google

severe headache. One brother, a pale and poorly developed lad, died at the age of 18 of "kidney trouble." The mother later stated that this boy's illness was very similar to his sister's, and that death occurred in the same manner. Otherwise the family history was negative. The patient had whooping cough at the age of 2 and measles at 4, but no other infectious diseases, and had always enjoyed fairly good health. The menses were established at 13, but had not been present since September, 1921.

The present illness began in the latter part of September, 1921, with pain in the left side of the back that had a tendency to radiate to the groin. With this she had chills and fever, and was confined to bed for two weeks. Since then she had been up and about, but had not felt well enough to go to school. Occasionally she had chilly sensations and pain in the back at night. During the two weeks prior to admission, she had a recurrence of her former symptoms; pain in the left flank, severe headache, attacks of vertigo, nausea and vomiting, and marked burning on urination, but a decreased frequency. She voided only once daily, and then only a small amount of dark colored urine. There was edema of the face in the morning, which disappeared later in the day.

She was pale and moderately well developed; the temperature, pulse and respiration were normal. The blood pressure was 120 sytolic, and 80 diastolic. The urine had a specific gravity of 1.010, a heavy cloud of albumin, red and white blood cells in abundance, and occasional hyaline and granular casts. Blood examination revealed: hemoglobin, 43 per cent.; red blood cells, 1,980,000; white blood cells, 20,300. The blood nitrogen retention, December 18, was very marked; the urea nitrogen, 240 mg.; the nonprotein nitrogen, 300 mg., and the creatinin, 3.1 mg. The eyeground examination was negative. Urine culture demonstrated the colon bacillus.

Cystoscopy revealed the left ureteral orifice normal; the right, slightly inflamed; ureteral catheterization was unsuccessful. The indigocarmin test indicated no excretion from either side in twenty-five minutes.

Roentgen-ray examination disclosed considerable gas in the abdomen blurring the outline of the kidney. There was a dense calcareous shadow in the region of the right upper abdomen.

During her ten days in the hospital, the patient voided only 3.5 liters of urine. She became progressively weaker, more and more stuporous, and died, December 23.

Necropsy, limited to the abdomen, was performed the same day. Both kidneys were small, each weighing 70 gm. The capsule of the left kidney stripped readily, leaving a finely granular, grayish-red surface; the organ cut with markedly increased resistance; the cut surface was pale and the cortex

Digitized by Google

uniformly narrowed; the pelvis and ureter appeared normal, and the renal vessels were smooth and soft. The right kidney was very similar in appearance, but had a dilated pelvis that was intensely inflamed, and contained a stone, which measured 3 by 2.8 by 1.5 cm. The ureter was also dilated and inflamed.

Microscopically, the kidneys were extensively fibrosed. The glomeruli, except for the swelling due to dilated capillaries, seemed but little affected, although the capsules of Bowman were almost universally greatly thickened. A striking feature was the presence, in many of the tubules, of calcific deposits that stained deeply purple. These occurred in the lumina or in the epithelial cells. Tubules in all parts of the kidney, from capsule to pelvis, were affected, and the process was even more pronounced in the right kidney. The pelvis of the right kidney was fibrous, showed leukocytic infiltration, and had lost most of its epithelial covering. The right ureter also showed desquamation of epithelium, and the lumen contained epithelial cells, leukocytes and many masses of calcareous substance.

The condition of the patient was diagnosed as chronic interstitial nephritis associated with extensive tubular deposits of calcium salts, and nephrolithiasis of the right kidney, pyelitis and ureteritis.

Summary: The finding of small, fibrosed kidneys with considerable calcific deposit[2] in a girl of 15, who had shown a rapidly progressive loss of kidney functional power with no previous infection worthy to be considered a causative factor, and a history of a similar condition in a brother who died at the age of 18, strongly suggest a congenital basis. This hypothesis becomes even more attractive if we assume that, although her kidneys had been below par since birth, they were capable of meeting the ordinary demands of kidney function, and showed functional incapacity only when subjected to the strain induced by a large kidney stone and an associated infection.

COMMENT

While frequent references have been made to hereditary and congenital factors in arterial disease, insufficient attention has been paid, in my opinion, to the same factors in the determination of a renal lesion. Coplin,[3] however, has for many years contended that

2. Kidd made a similar observation in a study of Bright's disease extending through three generations (The Inheritance of Bright's Disease of the Kidney, Practitioner, London **29**: 104, 1882). He found extensive calcium deposits in the kidneys in two cases of chronic renal disease occurring in young persons.

3. Coplin, W. M. L.: Unilateral Renal Hypoplasia and Dysplasia Due to Defective Arteriogenesis; Relation to So-Called Hypogenetic Nephritis, Am. J. M. Sc. **153**: 381 (March) 1917.

Digitized by Google

there is a type of renal anomaly of developmental origin which predisposes to, or renders inevitable, some form of nephritis. He refers particularly to hypogenesis, and believes that the original fault is probably primarily a defective arteriogenesis. He concludes that nephritis or uremia coming on in young persons without adequate cause should arouse our suspicion of this type of renal lesion.

Ringer,[4] from a clinical point of view, expresses his dissatisfaction with our present views in regard to the etiology of nephritis, stating as his belief that the various infections and intoxications which are usually held to be responsible play but a secondary rôle, i. e., merely an exciting rôle, and that the primary seat of trouble lies in the kidney itself. He says, "We can readily conceive of organs in the human body at birth being of functional capacity below par." He quotes Stockard as saying: "Every person dies from the disease with which he is born, . . . and . . . during the period of differentiation the organ is marked out which is the weak link in the chain." Ringer then concludes that, so long as the individual remains well, the renal condition goes unrecognized; but any insult, in the form of infection, or any strain, as pregnancy, may cause a break in the weak link, with the onset of a clinically recognizable nephritis.

Babes[5] has observed six cases of chronic renal disease occurring in young, frail and anemic subjects, usually under the age of 30, with no history of previous nephritis or conditions supposed to cause nephritis. In each case, a slight infection precipitated a sudden grave uremia, with coma and death in a few days. In a discussion of the kidney findings at necropsy, he mentions an excessive diminution of volume and certain characteristics of indurated and granular atrophy, or

4. Ringer, A. I.: Chronic Nephritis, from the Point of View of the General Practitioner: Its Diagnosis, Prognosis and Treatment, Am. J. M. Sc. **161**: 798 (June) 1921.

5. Babes, V.: La néphrite hypogénétique, Semaine méd. **25**: 63 (Feb. 8) 1905.

Digitized by Google

of arteriosclerotic kidney, differing essentially from the two forms or their combination. Therefore he states that in these cases it is not a question of ordinary sclerotic nephritis, of simple arteriosclerosis, of insufficiency of the arteries or of a combination of these pathologic processes, but rather a particular state of the kidney: a true hypogenesis. He believes that during the lifetime of the individual the kidneys are at the limit of their capacity, and that a comparatively minor infection results in a fatal uremia. He concludes that one must think of a nephritis grafted on a hypogenetic kidney if, in a young poorly developed subject without renal antecedents but with hypertrophy of the heart, a fulminating uremia follows a slight malady.

CONCLUSION

It is impossible, of course, to be certain regarding the etiology of the renal lesion in the three cases on which this report is based. It does seem, however, that they correspond closely to those outlined by Babes. The subjects may therefore be regarded as individuals congenitally predisposed to the development of a renal lesion, probably because of a "weak link" (hypogenetic kidneys) in the cardiovascular-renal chain, with a determining factor in the form of an infection or strain resulting in the rapid onset of a fatal uremia.

It is obvious that such a suggestion, partly based on the gross and microscopic appearance of the kidneys, is not in keeping with the modern clinical classification of nephritis on a functional rather than a structural basis. But I do not believe we are wholly justified in disregarding the appearance of the kidneys at necropsy and, although the justice of the present day clinical classification is acknowledged, still it is to be regretted that the tendency is away from the pathologic basis, which is necessary for a just conception and further progress in the study of disease.

1906 Walnut Street.

Digitized by Google

SOME RECENT ADDITIONS TO THE KNOWLEDGE OF ASCARIASIS *

B. H. RANSOM, PH.D.
WASHINGTON, D. C.

Before this Association at its session three years ago, I [1] called attention to the striking discovery made by Stewart [2] relating to the life history of the common roundworm, *Ascaris lumbricoides,* and gave some of the results of investigations on the same subject carried on by Foster and myself subsequent to Stewart's important discovery. Stewart had observed, as Davaine had done fifty years earlier, that when the eggs of this parasite in their final development were fed to rats and mice, they hatched out in the small intestine. A few hours after feeding the animals, he recovered free larvae in the feces, also in confirmation of Davaine's observations.

In addition, however, to the confirmation of these long known and comparatively insignificant facts, Stewart demonstrated that not all of the newly hatched larvae thus passed out of the body. From four to ten days after feeding his experimental animals with *Ascaris* eggs, he detected larvae in later stages of development in the liver and lungs. He observed also that rats and mice that had been fed large numbers of *Ascaris* eggs developed pneumonia within a few days after feeding, and usually died before the tenth day. Further, he observed a migration of the larvae from the lungs after they had reached a length of from 1 to 2 mm., up the trachea and then down the esophagus to

* From the United States Bureau of Animal Industry.

1. Ransom, B. H.: A Newly Recognized Cause of Pulmonary Disease —Ascaris Lumbricoides, J. A. M. A. **73**: 1210-1212 (Oct. 18) 1919.

2. Stewart, F. H.: Life History of Ascaris Lumbricoides, Brit. M. J. **2**: 5-7 (July 1) 1916; Life History of Ascaris Lumbricoides, ibid. **2**: 474 (Sept. 30) 1916; Further Experiments on Ascaris Infection, ibid. **2**: 486-488 (Oct. 7) 1916; Life History of Ascaris Lumbricoides, ibid. **2**: 753-754 (Dec. 2) 1916.

Digitized by Google

the stomach and intestine. The larvae, thus returning to the intestine a week to ten days after the feeding of the eggs from which they hatched, lingered a few days in the intestine, particularly in the cecum, and finally passed out of the body in the feces without undergoing further development.

Having failed in two attempts to rear adult worms in the intestines of pigs by feeding them *Ascaris* eggs, Stewart, in interpreting the results of his experiments on rats and mice, suggested the possibility that these animals act as intermediate hosts of *Ascaris,* becoming themselves infested by swallowing the eggs scattered in the feces of human beings and pigs and, in turn, by contaminating food and drinking water with their own feces, passing on the parasites, after a partial development, to human beings and swine. From a hygienic standpoint, this hypothesis, if it were substantiated, would of course be of great importance because of its direct bearing on the question of the prevention of ascariasis. As a result, however, of other work[3] following Stewart's earlier experiments, some of which was mentioned in my paper of three years ago and concerning which a number of publications have since appeared, it may now be accepted as definitely established that rats and mice play no part as normal intermediate hosts in the life history of *Ascaris.*

The conception of the life history prevailing before Stewart's discovery has not yet been shown to require any modification so far as concerns the manner of spread of the parasites from one human being or pig to another. It is quite certain that *Ascaris* has a direct life history and that no intermediate host is required. Our present conception of the life history, however, differs from the former in that we now know, thanks to the work of Stewart, supplemented by that of other investigators who have interested themselves

3. Ransom, B. H., and Foster, W. D.: Observations on Life History of Ascaris Lumbricoides, Bull. 817, U. S. Dept. Agric. (May 12) 1920; Stewart, F. H.: On Life History of Ascaris Lumbricoides L., Parasitology **13**: 37-47 (March) 1921.

Digitized by Google

in the subject, that the newly hatched worms, instead of simply settling down in the intestine of the human being or pig to undergo their development to maturity, first leave the intestine, pass to the liver and then to the lungs in the blood and lymph circulations, and finally come back again to the intestine by way of the trachea and esophagus just as they would do in a rat or a mouse. The essential difference in the two cases is that in the human being or pig the larvae, when they return to the intestine after having undergone a partial development during their tour, are able then to continue their development and to reach fertile maturity, which they cannot do in a rat or mouse, or in a guinea-pig or a rabbit. It has been shown that in guinea-pigs and rabbits the larvae behave as they do in rats and mice.

Lambs and young goats occupy an intermediate position, in their adaptability as hosts, between the smaller animals that have been mentioned and the more completely adapted hosts, man and the pig. It has been experimentally shown [4] that, in lambs and young goats, the larvae that return to the intestine after their migration through the lungs may settle down and continue their development. This development, however, at least in the case of lambs, is very slow, and apparently the worms never reach fertile maturity. From our present knowledge, it is clear that the so-called *Ascaris ovis* of sheep is nothing more than *Ascaris lumbricoides* in an unusual host. Sheep, however, are of no evident hygienic importance as carriers of the parasite, as indicated by the fact that the females of *A. ovis* have been examined in a considerable number of cases of infestation but have never been found to contain fertile eggs. In the spread of *Ascaris,* the only carriers that need be considered as of practical importance are the two common hosts of the adult parasite, man and the pig.

The roundworm of man and the roundworm of the pig are certainly of the same species. They have repeat-

4. Ransom, B. H., and Foster, W. D.: Footnote 3, first reference).

Digitized by Google

edly been compared morphologically, and no differences have been established. Also, in complement fixation tests Bakker [5] has found that the roundworms of the pig and man act reciprocally in an identical manner. It is barely possible that the two forms represent distinct races or varieties, each of which is specifically adapted to its own host and unlikely, if not unable, to live in the other. Instances of such adaptations among parasites are well known. For example, among the scab mites in some genera there are forms, variously interpreted as species or varieties, that cannot be distinguished from one another by morphologic differences, yet these similar forms are more or less strictly limited to their own host species and in some cases cannot live at all on a strange species of host, though this host may be subject to infestation with an apparently altogether similar parasite. From a hygienic standpoint, it is evident that such biologic differences in host relationships are of the highest importance. In the case of ascariasis, however, even if we admit that the human *Ascaris* and the pig *Ascaris* are sufficiently different biologically to prevent a successful interchange of the parasites in either direction between man and the pig —in other words, if we assume that the pig need not be taken into practical consideration in the prevention of human ascariasis and, conversely, that the parasites cannot spread indifferently from man to the pig, there are nevertheless good reasons, which have come out of the work of recent years, why ascariasis of pigs must be given consideration in human hygiene.

The migration of large numbers of larvae of *Ascaris* through the lungs, it has been proved,[8] may produce pneumonia not only in small laboratory animals, but also in pigs, and in addition to other possibilities of injury, the possibility is not at all excluded that such invasions, even when very slight, may be the effective means of bringing about or preparing the ground for

5. Bakker, C. R.: Over de Identiteit van Ascaris Lumbricoides en Ascaris Suilla, Tijdschr. v. Vergel. Geneesk. 6: 160-230 (May 30) 1921.

Digitized by Google

a serious superimposed infection by other organisms, either coincidental with the worm invasion or following it, perhaps even after a long interval. The occurrence of more or less serious lung trouble as an immediate result of invasion by *Ascaris* larvae has been repeatedly demonstrated experimentally in pigs, and altogether similar occurrences have been common in the field. Many of the cases of so-called thumps, a very prevalent malady among pigs, are caused primarily by *Ascaris* larvae in the lungs. That pulmonary ascariasis of a more or less severe form occurs also among human beings cannot be doubted. In fact, one or two cases in young children, apparently of pulmonary ascariasis, have been mentioned in the recent literature,[6] and it is of interest to note that Mosler in 1867 and Lutz in 1888, long before Stewart's discovery of the migration of *Ascaris* larvae in small experimental animals, recorded the occurrence of pulmonary symptoms in human beings following the experimental administration of *Ascaris* eggs. In the light of our present knowledge it is very probable that these symptoms were the result of the invasion of the lungs by migrating *Ascaris* larvae.

It is true that human beings, because of their mode of life and their food habits, are less likely than pigs to ingest a sufficiently large number of *Ascaris* eggs at one time to cause a heavy invasion of the lungs by the larvae, but the possibility of such an occurrence is not remote, especially in the case of children exposed to close contact with soil that has been heavily polluted by feces either of human beings or of swine. So far as the invasion of the human lung by *Ascaris* larvae is concerned, it is proper to assume, for all practical purposes, that it makes no difference whether the parasites are of human or of suilline origin. Hence, in reference to pulmonary ascariasis, the conservative

6. Steiner, G.: Neure Forschungsergebnisse über die Lebensgeschichte der Ascaris Lumbricoides und ihre medizinische Bedeutung, namentlich als Ursache von Pneumonie, Schweiz. med. Wchnschr. **50**: 334 (April 22) 1920.

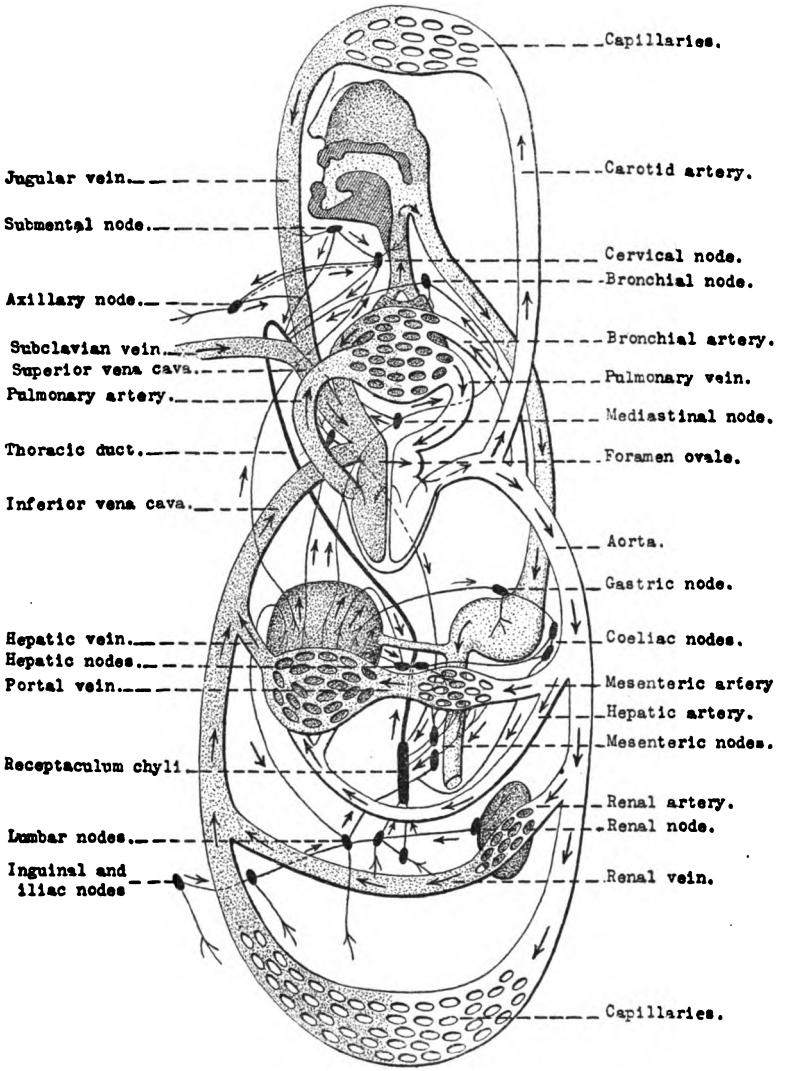
Digitized by Google

hygienist must take the position that heavy fecal contamination of the soil is likely to be equally dangerous to human beings, whether the contamination originates from human beings or from pigs.

In view also of the suggested possibility that very slight invasions of the lungs by *Ascaris* larvae may be followed more or less remotely by serious secondary or indirect consequences, it is evident that the protection of human beings from ingestion of even small numbers of the eggs of the pig *Ascaris* is a matter of potential hygienic importance, irrespective of whether such ingestion results in the development of egg-producing adult worms in the intestine. Moreover, the invasion of the liver, spleen, lymph nodes, thyroid, brain, kidneys and other organs besides the lungs by *Ascaris* larvae affords an additional reason for avoiding the ingestion of the eggs in either large or small numbers, not merely of the human *Ascaris* but also of the pig *Ascaris*.

How the larvae reach these various locations is indicated by the accompanying diagram. The larvae that hatch out in the small intestine, after the eggs containing them have been swallowed, promptly enter the wall of the intestine; they then pass to the liver in the portal circulation and, after crossing the capillary zone of the liver lobules, enter the central veins, by which they reach the hepatic veins, vena cava and right side of the heart. The newly hatched larvae measure about 0.25 mm. in length and about 0.012 mm. in diameter. They may pass rapidly through the liver or be delayed for several days, in the latter case undergoing growth and development, before they continue their journey. Some larvae may be permanently stopped in the liver, become encapsulated and die there. From the right side of the heart, the larvae are carried to the lungs, in which they enter the air sacs. Finally, after having developed to a length of from 1 to 2.5 mm. they pass up the trachea and down the esophagus through the stomach to the intestine, and develop to maturity in

Digitized by Google



Scheme of circulation: Arrows indicate direction of blood and lymph flow, and paths of migration of Ascaris larvae, including both theoretically possible and proved paths.

Digitized by Google

about two months. Some larvae that reach the lungs, however, apparently again return to the heart, and are then distributed to various parts of the body in the peripheral circulation. They may be recovered from peripheral lymph nodes as early as twenty-four hours after the eggs from which they hatched have been swallowed, and have been found still alive in such locations as late as thirty days after infection. Fülleborn[7] has recovered them from the brains of experimental animals.

In cases in which there is an open foramen ovale, it is theoretically possible that the larvae may reach the peripheral circulation by passing directly from the right to the left side of the heart without going through the lungs. The presence of the larvae in the peripheral lymph nodes of experimental animals in whose hearts the foramen ovale was closed would seem to preclude the possibility of their direct passage from the right to the left side of the heart, and force the conclusion that they had passed through the lungs. As to the possibility that the larvae in peripheral lymph nodes might have followed the lymphatics exclusively, it is inconceivable that in a few hours they could have worked their way for the distance they would have to travel by this route against the lymphatic current and past intervening lymph nodes and the valves of the lymph vessels. It should be mentioned that some larvae that hatch in the intestine, instead of passing directly to the liver in the portal system, find their way in the lacteals to the mesenteric nodes; some of the larvae that reach these nodes succeed in escaping from them, in some cases perhaps passing to the liver in the portal circulation, in other cases perhaps to the chyle receptacle in the lymph circulation and then, of course, to the right side of the heart by way of the thoracic duct, these two alternatives appearing more likely than that

7. Fülleborn, F.: Ueber Ascaridenlarven im Gehirn, Vorläufige Mitteilung, Arch. f. Schiffs. u. Tropen-Hyg. **25**: 62-63.

Digitized by Google

the larvae escape into the body cavity. Details of the experiments in which the migrations of *Ascaris* larvae in the body have been followed step by step, have been given in another paper.[8]

Another point of importance which has been made evident by recent work on *Ascaris* is that in the case of pigs, and probably also in the case of human beings, though perhaps in less degree, it is the young animal which is most susceptible to *Ascaris* infection and also most liable to suffer seriously from pulmonary ascariasis.[3] As the pig grows older, more or less complete immunity generally develops within a few months, often to a considerable degree within a few weeks. In case such older pigs swallow infectious *Ascaris* eggs, the worms hatching in the intestine do not succeed in effecting their migration and development or, if some of them do succeed, they cause no conspicuous disturbance. Available evidence indicates that this immunity or resistance to infection is related to age rather than to earlier infections, the pig becoming more resistant because of increasing age and not because one invasion by the parasites has a protective action against later invasions. It is barely possible that there may be also an immunity of the latter sort, but age in itself is an important factor in the production of complete or partial immunity to *Ascaris* infection.

The decreasing susceptibility to *Ascaris* infection that comes with advancing age is an exceedingly important point in the control of ascariasis among pigs, and has been taken advantage of in the development of methods for preventing or minimizing worm losses.[9] By taking special precautions to protect the young pigs from infection until they reach an age of about 4 months, a very remarkable reduction in the losses of

8. Ransom, B. H., and Cram, E. B.: Course of Migration of Ascaris Larvae, Am. J. Trop Med. **1**: 129-159 (May) 1921; Course of Migration of Ascaris Larvae from Intestine to the Lungs, Anat. Rec. **20**: 207 (Jan. 20) 1921.

9. Ransom, B. H.: Prevention of Intestinal Worms in Pigs, J. A. Vet. M. A. **59**: 711-715 (Sept.) 1921.

Digitized by Google

young pigs from ascariasis and associated diseases has been accomplished on many farms in which formerly heavy losses occurred. Under usual farm conditions in which a plan of prophylaxis designed to protect pigs of all ages from infection would be practically impossible, a plan designed to give special protection to the young pigs has been found which is easily applicable and economically profitable. In the case of children, age immunity, if it may be so called, is evidently not so rapidly established and perhaps never so completely established as in the case of pigs. Moreover, the fact that among people living under fair sanitary conditions children as a rule are more likely to harbor roundworms and to be more heavily infested than adults may be more dependent on differences in habits involving greater exposure to infection in the case of children than on a difference from adults in their susceptibility to infection.

Age immunity to parasites commonly varies in the case of the same species of parasite with different species of hosts. For example, chickens are readily susceptible to and likely to be seriously injured by infection with the common gapeworm (*Syngamus trachealis*) only while still quite young.[10] Adult chickens rarely harbor gapeworms. On the other hand, turkeys of all ages show little difference in the readiness with which gapeworm infection may be brought about experimentally, and gapeworms may occur naturally in a high percentage of adult turkeys in the same localities in which none can be found in adult chickens, although common enough in young chickens in these localities as in turkeys of all ages. Because of these facts and because of other evidence, it would seem that the turkey is the natural host of the gapeworm, the host with which it has been the longer associated and on which its continued existence as a species is

10. Ransom, B. H.: The Turkey an Important Factor in the Spread of Gapeworms, Bull. 939, U. S. Dept. Agric., April 23, 1921.

Digitized by Google

particularly dependent, and that the chicken is merely an incidental host to which the gapeworm is rather poorly adapted and with which also its association has been comparatively recently established.

It is possible that the relationship of *Ascaris* to its two hosts is somewhat similar to that suggested in the case of the gapeworm. The differences in the adjustment of *Ascaris* to its two hosts are less marked, however, than the differences in the adjustment of the gapeworm; and although it seems probable, considered from an evolutionary standpoint, that of its two hosts, man is the older, better adapted and more essential host of *Ascaris lumbricoides,* and that the association of the parasite with the pig is more recent, more casual, and less adequate to its continued existence as a species, our present knowledge is too incomplete to justify the acceptance of such a view, except as a hypothesis for further examination. This hypothesis is advanced merely as a suggestion, which at this time it would be useless to attempt to support by argument, because the facts now available are not sufficient either to prove it or to disprove it. I have ventured to mention it, however, because, in addition to whatever value it may have as a working hypothesis, it may be useful from a practical standpoint in reminding us that the problem of *Ascaris* control is perhaps essentially more difficult in the case of man than in the case of the pig, and that even if due allowances are made for the evident differences between the two hosts in their habits and environmental relationships, there may be yet other and less apparent differences between the two, in the relation of host and parasite, that are profoundly important and of such a nature as to require much more stringent control measures to secure successful results in the one case than in the other.

Digitized by Google

CULTIVATION OF TRICHOMONAS

AND THE QUESTION OF DIFFERENTIATION OF THE FLAGELLATES *

KENNETH M. LYNCH, M.D.
DALLAS, TEXAS

Barring a limited number of special workers, the conception of the whole of the medical profession is probably confused no more by any question than that of the intestinal protozoa. That when a physician receives a report of the presence of any of these organisms, all sorts of symptoms and conditions are attached to this fact, and it is made the basis of diagnosis and treatment of the sick, is a point of wide application. The particular importance of this fact lies in the likelihood of such a finding confusing the issue and leading away from some other existing condition.

The recent war is responsible for exciting interest in, and spreading misinterpreted information about, intestinal protozoa. It stimulated the examination of feces to a much wider practice than existed before, and so intestinal protozoa are much more commonly encountered. One cannot even estimate the number of laboratory technicians who are responsible for all sorts of examinations employed by practicing physicians, very few of whom can differentiate between *Endameba histolytica* and *E. coli,* or between the several flagellates; and yet one has only to visit the offices of practicing physicians to obtain an idea that there are hundreds, if not thousands, of such people, who actually have the whole responsibility of such examinations. It is probably not far wide of the mark to say that the average laboratory worker knows only two terms

* From the Medical and Surgical Clinic, Dallas.

Digitized by Google

applied to intestinal protozoa: ameba and trichomonas; and the mere presence of either is considered sufficient evidence of its parasitism.

Of course, there is only one reason for this state of affairs—ignorance and confused information in the medical profession, and among laboratory people in particular. That this exists widely is perfectly evident from the attention given discussions of the subject, particularly before local or regional medical societies. Intestinal protozoa have been and are being blamed for every sort of human ailment. Physicians are energetically treating "amebiasis," when only harmless *Endameba coli* is present, and "flagellate infection," when *"Trichomonas"* is found; and one instance comes to mind in which a considerable number of cases of *Balantidium* infection—the *"Balantidium"* probably being some flagellate—have been reported from his private practice by a physician in a small town.

There is little excuse at the present time for confusing harmless *Endameba coli* with *Endameba histolytica,* or *Balantidium* with any intestinal organism; but, from the reading matter available to the general profession, there is little wonder that the status of the flagellates is confusing.

In order that judgment of the flagellates may be put on a rational basis, we may as well discard the bulk of medical literature of this country on the subject, especially when inaccurate identification of the organism is involved, since one cannot be certain which protozoon was dealt with. Even now, there is no general distinction made between *Trichomonas* and *Chilomastix,* and undoubtedly a large part of our literature concerns the latter instead of *Trichomonas.* It cannot be clear to the average person who is interested in the question whether there are one or more trichomonads in the intestine, or whether the *Trichomonas* of the vagina, mouth and intestine are one or different organisms; and that most common intestinal

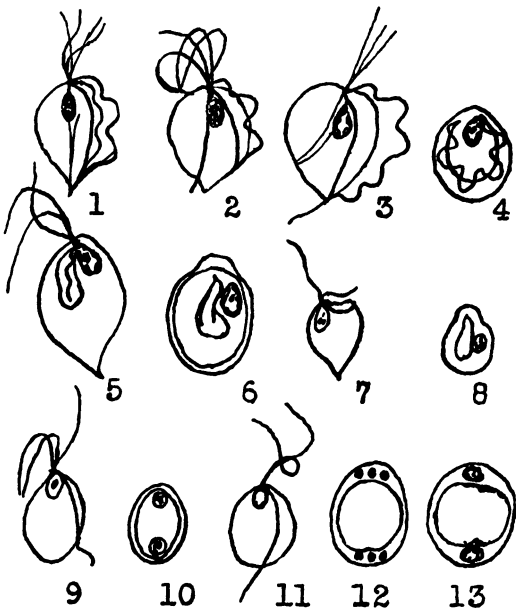
Digitized by Google

cell, *Blastocystis,* is not a *Trichomonas* or some other cyst. If we are to settle satisfactorily the clinical significance of *Trichomonas,* we must first be able to know it. Those who would determine the importance of the flagellates as a whole forget the history of the amebae and would not profit by its lessons. The terms "flagellosis" and "flagellate infection" have no meaning at the present time beyond the presence of flagellates.

Trichomonas is a common inhabitant of the large intestine, vagina and mouth. It is encountered very often in feces from normal persons. Whenever it is present where there is diarrhea and a liquid stool, it may be prolific and show in enormous numbers in the feces. Particularly is this the case when intestinal exudation occurs, probably because it grows very well in such a medium even under artificial conditions. Consequently, it is but natural that its presence is coupled with intestinal inflammation. That it is concerned with the production of inflammation, there exists only circumstantial evidence. It has been seen within the tissues of the intestine without evidence of exciting a reaction there; and whether it entered before or after death of the host cannot be said. It has been reported from parts of the body which it may have reached through the blood stream. It has been reported to contain red blood cells, and this has been taken as evidence of its pathogenicity. Clinical reports appear commonly in which "flagellate dysentery" has disappeared under treatment, with the apparent disappearance of the flagellate. On the other hand, although one does not see it often reported, numerous instances are at hand in which *Trichomonas* was present in diarrhea and remained after the diarrhea subsided, with or without treatment. Other instances are at hand in which the intestinal condition ascribed to it remained after *Trichomonas* could no longer be found. Then, again, a number of cases of "cure" of *Trichomonas* infection have been encountered in

Digitized by Google

which the person still harbored *Trichomonas*. I have under observation several hosts of *Trichomonas* as well as *Chilomastix* who have shown the organism on repeated examination for several years, one for as long as nine years, and who have never experienced any disturbance from it; and in routine laboratory work it is very common to find *Trichomonas* in the feces of people who can give no reference to any ill effects from it. When such a large proportion of people harbor



1, Trichomonas hominis; 2, Trichomonas vaginalis; 3, Trichomonas caviae; 4, Trichomonas caviae cyst; 5, Chilomastix mesnili; 6, Chilomastix cyst; 7, Embadomonas intestinalis, according to Dobell; 8, Embadomonas cyst, according to Dobell; 9, Tricercomonas intestinalis; 10, Tricercomonas cyst with two nuclei, according to Dobell; 11, Enteromonas caviae n. sp.; 12 and 13, Blastocystis.

any organism, it is inevitable that it may be associated with some disease condition in a considerable proportion.

From time to time, experimenters have reported transmission of *Trichomonas*, with apparent infection. None of these experiments can be called conclusive.

Digitized by Google

I realized this after reporting such experiments. It is virtually impossible to select animals not already harboring trichomonads; and, even if it were possible, no reliance can be placed on results obtained from material or cultures containing bacteria.

Trichomonas in the vagina is commonly associated with leucorrhea, and in the mouth it grows in the material and exudates around the teeth and gums, in inflammation. In my observation, it has disappeared with the clearing up of these excellent mediums for its growth, and it may have no further significance.

CULTIVATION

Trichomonas was first cultivated in beef broth (Lynch [1]). Since that time, Ohira and Noguchi [2] have reported obtaining cultures of *Trichomonas* from the mouth in equal parts of ascitic fluid and Ringer's solution. Boyd [3] obtained a growth of *Trichomonas hominis* in a mixture of feces and physiologic sodium chlorid solution. Pringault [4] cultured *Trichomonas hominis* in Ohira and Noguchi's medium; Reufing [5] *Trichomonas vaginalis* in the same solution, and Hogue [6] *Trichomonas hominis* in a medium of egg albumin and Locke's solution. I have cultivated *Trichomonas* from the feces, vagina, mouth and urine (*Trichomonas* of vaginal origin) in a number of solutions,[7] including liquid blood serum, ascitic fluid, pleural fluid and ovarian cyst fluid, diluted from 1:4 to 1:10 with from 0.5 to 0.9 per cent. sodium chlorid solution, or

1. Lynch, K. M.: Trichomoniasis of the Vagina and Mouth, Am. J. Trop. Dis. **2**: 627, 1915; Clinical and Experimental Trichomoniasis of the Intestine, New York M. J., May 1, 1915.
2. Ohira, T., and Noguchi, H.: The Cultivation of Trichomonas of the Human Mouth (Tetratrichomonas hominis), J. Exper. Med. **25**: 341 (Feb.) 1917.
3. Boyd, M. F.: A Note on the Cultivation of Trichomonas Intestinalis, J. Parasitology **4**: 168 (June) 1918.
4. Pringault, E.: Étude biologique die Trichomonas intestinalis, Bull. de la Soc. Path. Exot. **13**, 1920.
5. Reufing, F.: Zur morphologie von Trichomonas vaginalis Donne, Arch. f. Protistenk. **17**: 347, 1921.
6. Hogue, M. J.: The Cultivation of Trichomonas Hominis, Am. J. Trop. Med. **1**: 211 (July) 1921.
7. Lynch, K. M.: Blastocystis in Culture, Am. J. Trop. Med., to be published; Cultivation of Trichomonas from the Human Mouth, Vagina, and from Urine, Am. J. Trop. Med., to be published.

Digitized by Google

with Ringer's or Locke's solution. Blood serum diluted with ten volumes of 0.5 per cent. sodium chlorid solution has been found fairly uniformly good. *Trichomonas* grows well at 37 C., at the bottom of a fairly long column of medium, and is best removed with a capillary pipet. Growth is usually progressive, and division of the organism may be followed for about four days, during which time swarms of organisms may be produced. After this period, the number decreases, and the flagellates usually disappear in a few days.

DIFFERENTIATION OF SPECIES AND OTHER ORGANISMS

At present, *Trichomonas hominis* (from the intestine), *Trichomonas vaginalis* (from the vagina) and *Trichomonas buccalis* (from the mouth) are generally considered to be distinct species. At least, they have not been certainly identified as the same. They present in common four anterior flagella arising from the blepharoplast on the anterior end, from which also come the basal rod and free margin of the undulating membrane, which runs diagonally backward, and the axostyle or stiff skeletal support. The nucleus, lying near the anterior end, is ovoid, composed of a compact chromatin mass in the nondividing forms, of loose chromatin network preliminary to mitosis and showing mitosis in division. There is some debate about the constancy of four anterior flagella for the genus, some describing three and some five. In my exeperience, four is the correct number, although not all may be seen, and more are often encountered in division. Occasionally, one with five is seen, but this fact may not be used as a feature for separating the genus in any thus far encountered in this study. There have been a number of accounts of a five-flagellated trichomonad (*Pentatrichomonas*), which consumes red blood corpuscles. Possibly, this is a distinct organism, and it should be watched for closely on account of its

Digitized by Google

suggested pathogenic significance. I have not encountered a form of *Trichomonas* from man which did not show fairly constantly four flagella, when properly studied.

In direct preparations, there often seems to be differences betwen the trichomonas of the vagina, mouth and intestine. That of the vagina frequently averages larger in size and is often less active in swimming about. Frequently, the undulating membrane is shorter and more delicate. Yet these features also occur among the organisms from one source. It has been impossible thus far to differentiate with certainty the trichomonads from the intestine, vagina and mouth, in culture in the same material. It appears, therefore, that, under the same conditions, they are identical. At any rate, if they are distinct, the differentiating feature has yet to be developed and will have to apply to organisms cultivated under the same environment.

As to the relation of human trichomonads to those of other animals, at least some of the latter appear to be distinctly different. *Trichomonas* of the mouse, guinea-pig, and frog all have three flagella. *Trichomonas caviae,* which, following Kofoid [8] is now properly called *Tritrichomonas caviae,* has a distinct encystment, the cyst showing nucleus, blepharoplast, undulating membrane, basal rod and chromatinic margin and axostyle, but no flagella. Its undulating membrane is much heavier; the nucleus is different, and it has not grown with the facility of *Trichomonas* of man in the same culture mediums. Dobell has described a cyst for *Trichomonas* (*Tritrichomonas*) *batrachorum,* and Wenyon a cyst for *Trichomonas* (*Tritrichomonas*) *muris,* while no reported cyst of *Trichomonas* of man has stood the test of critical investigation. There is as yet no proof of a carrier of *Trichomonas* of man among other animals.

8. Kofoid, C. A.: A Critical Review of the Nomenclature of Human Intestinal Flagellates, Cercomonas, Chilomastix, Tetratrichomonas and Giardia, Univ. of California Pub. in Zool. **20**: 145, 1920.

Digitized by Google

A cell frequently called *Trichomonas* cyst is *Blastocystis,* probably related to *Ascomycetes,* a very common cell in the intestine, which has been differentiated for some time by careful observers and recently cultivated by Barret [9] and Lynch.[7]

The organism most commonly confused with active *Trichomonas* is *Chilomastix mesnili, Chilomastix davainei* according to Kofoid,[8] and yet it is so distinct that one wonders that the confusion existed even with the best students for so long. *Chilomastix* has three flagella anteriorly directed, a distinct and heavily outlined cytostome or mouth and no undulating membrane save a very delicate flagellar organ within the cytostome. It is frequently spirally twisted, and swims in a distinct spiral without the flexibility of *Trichomonas.* In addition, it has a characteristic lemon-shaped cyst, containing the organism with its distinctive cytostome, first described by Lynch [10] who mistook it for *Trichomonas.*

In addition, there are two or more comparatively rare flagellates of the human intestine which may be confused with *Trichomonas* by those uninformed about them. These are *Tricercomonas intestinalis, Enteromonas hominis* and *Embadomonas intestinalis.* They are about half the size of *Trichomonas* and have no undulating membrane. *Enteromonas hominis,* according to da Fonesca,[11] possesses three anterior flagella, two directed forward and one back over the body but not adherent. No cyst has been reported for it. *Tricercomonas intestinalis* is described by Wenyon and O'Connor [12] with four anterior flagella, three directed forward, the fourth recurrent and adherent to the surface of the body for a part of its length. Dobell [13]

9. Barret, H. P.: A Method for the Cultivation of Blastocystis, Ann. Trop. M. & Parasitol. **15**: 113 (July) 1921.
10. Lynch, K. M.: Dauercystformation of Trichomonas Intestinalis, J. Parasitology **3**: 28 (Sept.) 1916.
11. Da Fonseca, O. O. R.: Sobre os flagellados dos mamiferos do Brazil: um novo parasito do homem, Brazil-Med. **29**: 281, 1915.
12. Wenyon, C. M., and O'Connor, F. W.: Human Intestinal Protozoa in the Near East, London, 1919.
13. Dobell, Clifford: The Intestinal Protozoa of Man, Dobell and O'Connor, New York, 1921.

Digitized by Google

thinks these two flagellates are the same. In my experience, *Tricercomonas* of Wenyon and O'Connor is present in this country, and, although *Enteromonas* of da Fonseca has not been seen, a flagellate conforming to his description found in the guinea-pig confirms the existence of the genus and its possible occurrence in man. *Embadomonas intestinalis* has two unequal anterior flagella, a comparatively large anterior cytostome and a cyst resembling that of *Chilomastix,* except that it is much smaller. Possibly *Embadomonas* may be confused with *Chilomastix,* although it is less than half the size, its jerky movements differ from the spiral of *Chilomastix* and its flagella differ in number and action.

STUDY OF SPECIMENS

A careful study of unstained material will serve to differentiate *Trichomonas* from any other organism. When fresh and active, the flagellar movements and undulating membrane are characteristic. After exposure and cooling, it loses the action of these parts and assumes a peculiar ameboid undulating form in which protoplasmic waves of broad and blunt or long and finger-like proportions progress, with diminishing size from anterior to posterior end. This is also characteristic. When it becomes a question of determining the number of flagella, for the possible dividing of the genus, the most careful staining is necessary. These fine structures may not be counted with certainty on the active cell, and the staining must be sufficient to allow correct observation of a large number of organisms and to differentiate those undergoing division. The usual process depended on for this differentiation is the iron-hematoxylon method. When properly applied, this staining is usually satisfactory, but it has not served so well with spreads from cultures, probably on account of the albumin to be coagulated in the mediums. Excellent results have been obtained in differentiating the flagella and undulating membrane

Digitized by Google

by careful staining of thin films from cultures by Wright's blood stain.

SUMMARY

1. *Trichomonas* is a widely and highly prevalent inhabitant of the body of man and is being extensively treated as a pathogenic organism.

2. There exists only circumstantial evidence of any harmful effects from it or even of its true parasitism. The ease with which it may be grown artificially, its feeding habits, its high prevalence in the healthy and its long continuance without resulting disturbance in the human body indicate it as a harmless commensal.

3. For a proper judgment of the clinical significance of *Trichomonas,* the organism must first be accurately differentiated from others now confused with it, and, if there are different organisms now included in the genus, they must be separated.

4. *Trichomonas* must be studied under the same conditions before they may be differentiated. This would appear to be best done in culture in the same mediums.

5. In culture in the same material, trichomonads from the human mouth, vagina and intestine have not been certainly differentiated in this study.

6. There exists no proof that trichomonads of other animals are identical with those of man, and at least some of them are certainly distinct.

ABSTRACT OF DISCUSSION

DR. JOHN A. KOLMER, Philadelphia: Did the parasites undergo any morphologic changes differing from the appearance as found in the mouth?

DR. KENNETH M. LYNCH, Dallas, Texas: There are no changes in cultures from the characteristic morphology in the direct preparation. Of course, the multiplying forms are much more easily studied.

Digitized by Google

ENDOCRINOLOGY

LEWELLYS F. BARKER, M.D.
BALTIMORE

This symposium on internal secretions includes several papers that deal chiefly with the physiologic, the pathologic and the therapeutic effects of endocrine substances. I have been asked to make, by way of introduction, some general remarks on the subject of endocrinology as a whole. A discussion of the topic is timely and should be of value to workers in every branch of medicine. The profession in general is evincing a lively interest in the internal secretions, as is shown by the titles of papers read at medical meetings. An association for the study of the internal secretions already has a large membership, and its special journal, *Endocrinology,* is widely read.

THE ENDOCRINE ORGANS

Organs of the body that yield to the blood, in addition to the common metabolites resulting from the general life processes of cells, certain specific products that influence distant parts have been designated "endocrine organs," and the special substances thus yielded are known as "internal secretions." These endocrine organs have sometimes been called the "glands of internal secretion" because their products are distributed to the circulating fluids of the body itself rather than to the world outside or to tubular canals that communicate with the external world. They have sometimes been called "ductless glands," to distinguish them from glands whose products emerge through epithelial lined channels; though it should be remembered that in some organs, like the pancreas, we have some parts producing an external secretion dis-

Digitized by Google

charged through a duct, and other parts producing an internal secretion that is discharged directly into the lymph or blood without the intermediation of a duct. Recently, the endocrine organs have been spoken of as "incretory organs," the specific substances they produce being known as "incretions," to distinguish them from the "secretions" and the "excretions" of other glands.

The principal endocrine organs are the thyroid, the parathyroids, the thymus gland, the lymph glands, the suprarenal glands, the gonads, the hypophysis cerebri (or pituitary gland), the epiphysis cerebri (or pineal gland), and the insular tissue of the pancreas (islands of Langerhans), though it is quite possible that other organs, as the spleen, the kidneys, the liver, the salivary glands and the prostate, also perform endocrine functions in addition to their other physiologic activities.

In agreement with the idea that the specific substances produced by the endocrine organs are carried by the blood or lymph to distant parts, modifying the activity of the cells there, the term hormone was suggested for these substances by Bayliss and Starling. It is quite possible, however, that some of these incretions, instead of acting as excitants or depressants of distant cells, as the hormones are supposed to do, perform the function of neutralizing poisonous substances circulating in the blood. Such hypothetic detoxicants have been designated "negative incretions," to distinguish them from true hormones, or "positive recrementitious incretions."

FUNCTIONS OF THE ENDOCRINE ORGANS

The ways in which the specific products of the endocrine organs influence the rest of the body are gradually being found out. Progress has been especially rapid since the more exact chemical nature of some of the specific substances produced has been discovered,

Digitized by Google

making it possible to apply more extensively experimental methods to the study of hormonal activities. Epinephrin, isolated from the chromaffin tissues, thyroxin from the thyroid, pituitary extract from the hypophysis cerebri, and, very recently, insulin from the islands of Langerhans of the pancreas, are notable instances of incretory substances, or extracts, useful for experimental work. Physiologic investigators, as well as pharmacologists, have been busily engaged in determining by animal experiment the influences of these substances, or extracts, when introduced by various routes, on the physiologic processes in the different organs and tissues. Clinicians are comparing, in diseased human beings, the effects of these purer substances or extracts with the effects producible by administration of the fresh, or dried, organ substance as a whole. It is scarcely conceivable that an endocrine organ produces only a single important substance, as thyroxin in the case of the thyroid or epinephrin in the case of the chromaffin tissue; it would seem probable that each gland may produce at least several substances, even though our attention may at present be focused on only one.

Many of our ideas concerning the functions of the individual endocrine organs have been derived from extirpation experiments in which the effects on the animal operated on have been noted and the curative influences of substitutive therapy (organ transplantation; dried gland administration) have been observed. Even more important, perhaps, have been the clinical-pathologic studies that have correlated either anomalies of constitution or disease syndromes with demonstrable pathologic-histologic alterations in the endocrine organs and with demonstrable physiologic or chemical evidences of overfunction or underfunction of those organs.

Sufficient knowledge has been gained by these and other methods to make it seem clear that the incre-

Digitized by Google

tions may act on distant cells in a modifying way either directly through transport through the blood to them, or indirectly through the intermediation of the autonomic nervous system. When they act directly, they may determine the way in which the energies and substances in the terminal cells are utilized (functional correlation), or they may supply substances that are actually made a part of the distant cells that receive them and use them for their nutrition or for structural change (formative influence). When they act indirectly through the intermediation of the autonomic nervous system, they may, by stimulating, favoring or inhibiting the fibers of that system, greatly modify the functions of the secretory and excretory organs of the body and of the involuntary musculature of the vascular, digestive, respiratory and urogenital systems.

Furthermore, either by direct stimulation of the nerve mechanisms concerned or by indirect influences on these mechanisms through the autonomic nervous system, endocrine products undoubtedly play an important rôle in the physiologic processes that are conceived of as running parallel to certain of the psychic functions, especially those that we designate as the affective and the conative. This relationship of the incretions to the psychic mechanisms would seem clear from clinical observation of pathologic emotivity and of pathologic behavior observable in various endocrine disorders, notably in exophthalmic goiter and in myxedema.

It is known, further, that profound effects are produced by certain of the incretions, especially those of the thyroid, the hypophysis and the gonads, through the regulation of the metabolic processes. Whether these effects, in turn, result from influences exerted directly by the hormones on the body cells or indirectly through the mediation of the autonomic nervous system must be left to further investigations to reveal. It would seem probable, however, that an acceleration of the

Digitized by Google

general metabolism, such as can be induced by an excessive thyroxin production by the thyroid gland, may be due to a direct hormonal influence on the processes of combustion within the body cells, though it is conceivable that the same effects might be produced indirectly through hormonal action on a hypothetic metabolism-regulating center; located, say, in the interbrain. Similarly, one might speculate regarding localized morphogenic effects, such as the growth of the acra in acromegaly, which could be due either to selective hormonal influences on local groups of distal cells concerned in the growth processes, or to selective hormonal influences on local groups of trophic neurons of the autonomic nervous system.

THE SO-CALLED HORMONOPOIETIC SYSTEM

The conception that the endocrine organs are linked together so as to form a system of reciprocally dependent organs (hormonopoietic system) has gradually gained general credence, not only among clinicians, but also among physiologists and pathologists. And it must be admitted that there is considerable evidence in favor of the existence of such a correlative interdependence among the several incretory glands. Physiologists, through their experiments, have adduced many facts that point to manifold interrelationships between the glands of internal secretion. And clinical-pathologic studies have shown that uniglandular endocrinopathies are rare, whereas pluriglandular endocrinopathies are common. In exophthalmic goiter, for example, we see not only diffuse hyperplasia of the thyroid gland but also, not infrequently, hyperplasia of the thymus as well as signs of insufficiency of the gonads. In Froehlich's syndrome, to cite another instance, we see not only the signs of a disorder of the hypophysis cerebri but also evidences of hypogenitalism. It seems very probable, therefore, that in the chemical integration of the bodily activities a certain cooperation among the

Digitized by Google

endocrine organs is essential. The hormonopoietic system is concerned as a whole. It, like the nervous system, helps to correlate the partial systems of the body into a harmonious unity.

EVOLUTIVE SIGNIFICANCE OF THE INCRETIONS

That the substances produced by the incretory organs are of great importance in the development of the individual, not only during embryonic life but also during the further evolution of the organism to the acme of its development, is now a generally accepted view. The ontogeny of the single organism depends on reactions that occur between the germ plasm of the fertilized egg cell, on the one hand, and the environment (prenatal and postnatal) on the other. The fertilized germ plasm, consisting of a complex of "gens," constitutes the so-called "genotype," which determines the modes of reaction that are manifested during development. Environmental influences (at first chemical and physical, later on also psychic and social) are the other factors that are concerned in the development of the single creature. The resultant of the interaction of these environmental influences on the one hand, and the inherited influences on the other, is the "realized organism," or, in the case of human beings, the "realized person." This realized person is sometimes spoken of as the "phenotype." The inherited or constitutional factors (genotype) are known as the "determination factors" in development, whereas the conditioning influences of the environment are known as the "realization factors" (Roux). The part contributed by the germ plasm to the phenotype is known as the "constitution" of the individual, whereas the part contributed by the environment to the same phenotype is known as his "condition."

Students of heredity have long been interested in tracing the mode of development of the realized qualities or traits from their potentialities in the gens. It

Digitized by Google

now seems clear that, in this evolutive process, hormonal substances derived from the endocrine organs are of prime importance. The functioning of the endocrine glands during development depends in part on their genotypic origin and in part on the modifying influences exerted on these glands at different stages of development from the environmental side. It seems probable that a more exact understanding of racial peculiarities, of normal constitutional types or personal variants, and of pathologic anomalies of constitution will depend on our acquiring a more precise knowledge of endocrine activities during development.

The general dimensions as well as the relative proportioning of the body are certainly in large part dependent on the incretions acting as morphogenic stimuli. These stimuli determine not only the development of the skeleton and the closure of the epiphyseal lines but also the development of the soft parts. In a word, both the form relations and the functional manifestations of the phenotype are largely the result of endocrine activities. The origin of the bodily features and a whole series of local and temporal maturations depend in the developing individual on a correlative differentiation that is largely determined by the functioning of the endocrine glands. The special species characters, the special age characters, and the special sex characters of the realized person find their explanation here. So, too, the strange faults of composition of the human body, the various bizarre anomalies of constitution that we see, apparently owe their origin to endocrine disharmonies of the earlier developmental periods, disharmonies that are usually of genotypic origin, though they may sometimes, perhaps, be due to extraconstitutional, or so-called conditional, abnormalities.

The task of the endocrinologist in unraveling the specific influences of the single endocrine glands on growth and development is one of extreme complexity,

Digitized by Google

but nevertheless one in the solution of which gratifying progress is being made. How far during intra-uterine life incretions derived from the mother (so-called "harmozones" of Gley) may reach the fetus and participate in morphogenesis (normal or pathologic) is a further task in which students of constitution and condition must sooner or later become interested.

INVOLUTION AND ITS ENDOCRINE RELATIONSHIPS

After the body and the psyche reach their acme of development as the result of a long series of evolutive processes, a reverse process gradually sets in, both body and mind being subject, no matter how good the constitution or how favorable the environment, to gradual but progressive involution. Physical and mental endurance lessen; the hairs grow gray or fall out; the skin becomes wrinkled; the teeth fall out; the stature lessens; the metabolic processes become retarded; interests change; desires begin to fail, and memory becomes uncertain. In other words, the person "grows old." Coincident with the appearance of these involutive phenomena there seem to be changes not only in the endocrine glands themselves but also in the terminal organs on which their products operate. In pathologic constitutions, in which the complex of gens in the genotype has been deficient, one or more of the involutive phenomena may prematurely appear. Doubtless, too, persons of normal constitution who have been exposed over a prolonged period to very unfavorable environmental influences may become the victims of a precocious senium. Some of the so-called heredofamilial diseases of the nervous system are probably examples of premature involutive processes affecting partial constituents of the organism, though how far, if at all, abnormal endocrine functions are responsible, we do not yet know. Exact studies of the various processes of involution and their relations to the incretions will provide an abundance of work in the future for investigators of normal and pathologic physiology.

Digitized by Google

CLINICAL RECOGNITION OF ENDOCRINE ABNORMALITIES

The clinical recognition of the endocrinopathies has been greatly aided by the observation of human beings in whom single glands have been removed surgically, have been severely traumatized, or have suffered destruction by disease. The findings in human beings have been manifoldly corroborated by experiments on animals. The studies of myxedema due to loss of the thyroid, of tetany due to loss of the parathyroids, of dystrophia adiposogenitalis due to injuries of the hypophysis, eunuchism due to loss of the gonads, of Addison's disease due to destruction of the suprarenals, and of diabetes mellitus due to injury to the islands of Langerhans, have thrown a flood of light on endocrine domains. Studies of overfunction and of dysfunction have been similarly rewarding. But various permutations and combinations of symptoms and signs that are possible in complex endocrinopathies make their study exceptionally difficult. We are only on the threshold of that knowledge that we hope ultimately to possess.

THERAPY OF THE ENDOCRINOPATHIES

Though the principles of therapy for the endocrine diseases are not hard to grasp, the application of these principles in practice is compulsorily restricted, owing to the fragmentary character of existing knowledge. When, through constitutional deficits, or through unfavorable conditional influences, disharmonies of the hormonopoietic system arise, and evidences of hyperfunction, of hypofunction or of dysfunction, of one or more of the single endocrine organs appear, therapeutic intervention may become desirable. Thus, in the various constitutional anomalies that seem to be dependent on endocrine imbalance, prophylactic measures may be undertaken with the object of maintaining the subjects of these anomalies within the limits of normal responsivity. We attempt by adequate measures

Digitized by Google

to counteract in such persons the special disposition to disease that the constitutional anomaly entails. When a disease process has already developed, in other words, when an endocrinopathic personal variant has become incapable of satisfactory adaptation (state of irresponsivity), the physician may attempt to decrease function here, to increase function there, or to modify function elsewhere, in the hope of restoring balance, and of bringing the powers of personal adaptation again within the limits of normal responsivity. Thus, in hyperfunction of an endocrine organ it may be desirable to excise a portion of it, or to curtail its activity by diminishing its blood supply (ice-bag; arterial ligation); or, by means of a depressive radiotherapy or chemotherapy. On the other hand, in the case of hypofunction, it may become desirable to resort to organ transplantation, or to a substitution therapy (administration of gland substance, or of gland extracts, or of isolated hormones), or to attempt to revive a failing function by a dietetic hygienic regimen, or by mild stimulative radiotherapy.

The field for endocrine therapy is undoubtedly a large one, but how most effectively to work in it, we must slowly and painstakingly ascertain. Relatively little is gained, and much harm can be done, by reckless, ill-planned, fumbling attempts at incretory therapy. Much better is it to proceed patiently, cautiously and methodically, rigidly controlling every step, and faithfully recording our failures as well as our successes. Only slowly will it be possible to acquire the knowledge and the technic that will permit a physician properly to help the single endocrinopathic patient. As yet we are far from being able satisfactorily to disentangle in a given person the complex, interacting determination factors and conditioning factors that account for a given endocrinopathy. Adequate disentanglement of these factors is, however, the goal toward which we must strive.

Digitized by Google

SOME CONDITIONS CONTROLLING INTERNAL SECRETION *

W. B. CANNON, M.D.
BOSTON

No one may now question the great influence of the glands of internal secretion on important physiologic processes. The growth of the body, the proper development of the nervous system, the appearance of secondary sex characters, the orderly sequences in the reproductive cycle, the nature and rate of chemical changes in the body—all these fundamental processes seem to be in the grip of the endocrine organs. Agents which can determine whether an individual shall be a giant or a dwarf, an idiot or a normally intelligent person, a "sissy" or a real male, a bearded lady or a woman; agents which are essential to normal metabolism—indeed, whose destruction may lead promptly to death—must evidently be respected.

There appears to be a tendency just now, however, to pay these glands not only respect, but reverence and homage and a blind worship. The endocrine organs are referred to as "regulators of metabolism" and as "regulators of personality," as if they occupied an imperious position in our internal economy, and the other organs were mere servants to do their bidding. This is a concept which is largely based, I believe, on the marked effects of either the destruction of endocrine glands or the development of tumors and other pathologic states within them. When a gland is destroyed it is gone forever, and its absence tells us nothing about how it worked or the modulations of activity it may have had. On the other hand, tumors

* From the Laboratories of Physiology of the Harvard Medical School.

Digitized by Google

are dictators in relation to the rest of the body, living riotously outside the law.

Thus, two extreme conditions, neither of them normal nor even remotely physiologic, have led to the assumption of an endocrine almightiness. Is that the mode of organization of the body? Is our internal government autocratically ruled by a czar or a kaiser or by groups of kings and princes, represented by the ductless glands, or is there a more democratic arrangement whereby influences pass to and fro among the various parts of the organization and, after many mutual adjustments, finally express themselves in function?

The physiologist regards the body in the latter sense —as a system of organs, each performing its service, each influenced by other organs and capable in turn of influencing other organs, and each having a use and a value only in relation to the others.

Questions now arise regarding the real status of the glands of internal secretion. If they have not the dominant position commonly assumed for them, how may they be subordinated? What influences can be brought to bear on them in such a way as to modify their activity? These are important questions to have answered—important because of the profound effects which the ductless glands themselves are capable of exerting. In a brief survey I propose to present some of the evidence for physiologic control of the internal secretions.

EVIDENCE FOR NERVOUS CONTROL

We now have evidence that at least the suprarenal medulla, the liver and the thyroid gland are subject to sympathetic nerve impulses. Stimulation of the splanchnic nerves causes a discharge of epinephrin from the suprarenal glands into the blood stream in an amount which markedly affects other organs. Such stimulation also liberates sugar from the liver.

Digitized by Google

Uridil and I [1] have shown that under stimulation the liver yields another substance which raises blood pressure and causes an acceleration of the denervated heart. Furthermore, Smith and I [2] recently described experiments that confirm earlier work and testify to the efficacy of cervical sympathetic stimulation in calling forth a secretion from the thyroid gland.

It is well known that the sympathetic division of the autonomic system is brought into action by pain, asphyxia and great emotional excitement. That the three endocrine organs mentioned above may be strongly influenced by such conditions has been proved by numerous observations made both on experimental animals and in clinical cases. Extra epinephrin circulating in the blood when a sensory nerve is stimulated or signs of rage are evoked can be demonstrated by a faster beat of the denervated heart.[3] Emotional hyperglycemia or glycosuria, due doubtless to extra sugar freed from the liver, has been observed in cats disturbed by barking dogs, in students undergoing severe examination,[4] in aviators,[5] and in citizens terrorized by bombardments and air raids.[6] The thyroid likewise may be stimulated by painful and asphyxial conditions. Smith and I were able to obtain quite as striking results by such stimuli as we obtained by direct excitation of the cervical sympathetic strand. The considerable number of cases of exophthalmic goiter reported as occurring in consequence of stressful circumstances during the war [7] may perhaps be taken as additional indication of an influence on the thyroid gland exercised by the sympathetic nervous system.

Another gland which may be affected by nerve impulses is the posterior lobe of the pituitary. Weed,

1. Cannon, W. B., and Uridil, J. E.: Am. J. Physiol. **58**: 353 (Dec.) 1921.
2. Cannon and Smith: Am. J. Physiol. **60**: 476, 1922.
3. Cannon, W. B.: Am. J. Physiol. **50**: 399 (Dec.) 1919.
4. Folin, Denis and Smillie: J. Biol. Chem. **17**: 519, 1914.
5. Marañon, G.: Siglo. méd. **66**: 573 (July 19) 1919.
6. Etienne and Richard: Revue méd., Oct. 12, 1918.
7. Marañon, G.: Ann. de méd. **9**: 81 (Feb.) 1921.

Digitized by Google

Cushing and Jacobson [8] have reported that stimulation of the superior cervical sympathetic ganglion induces glycosuria (even though all nervous connections with the abdominal viscera have been severed), and that the result fails to occur if the posterior lobe of the pituitary has previously been removed. In harmony with this result is Shamoff's testimony that the same stimulation induces, besides glycosuria, such diuresis as is induced by pituitary extract.[9] The inference that a hormone is discharged from the pituitary as a result of stimulation has been somewhat invalidated by Rabens and Lifschitz,[10] who were unable to produce glycosuria by stimulating under physiologic conditions or to modify the glycosuria due to ether. Furthermore, though Keeton and Becht [11] did augment the reducing substance in the blood by direct excitation of the pituitary, the effect was abolished by severance of the splanchnic nerves. A nervous control of secretion from the posterior lobe of the pituitary is therefore in question.

Thus far, attempts to prove that internal secretion of the pancreas is subject to sympathetic impulses have proved futile. Allen [12] has testified to his inability to secure any indication of such nervous control, and von Noorden [13] has declared that he has not seen any influence of the excitements of war in producing true diabetes. Indeed, in the Central Empires, where the food shortage was marked, the deaths from diabetes were fewer toward the end of the war, despite the increasing nervous stress, than they had been at the beginning.[14] According to de Corral,[15] however, stimulation of vagus fibers below the branches to the heart results in a reduction of the sugar content of the blood.

8. Weed, Cushing and Jacobson: Bull. Johns Hopkins Hosp. **24**: 40, 1913.
9. Shamoff, V. N.: Am. J. Physiol. **39**: 279 (Jan.) 1916.
10. Rabens and Lifschitz: Am. J. Physiol. **36**: 47, 1914.
11. Keeton and Becht: Am. J. Physiol. **39**: 109, 1915.
12. Allen, F. M.: J. Metabol. Res. **1**: 53 (Jan.) 1922.
13. Von Noorden, C.: Med. Klin. **12**: 991 (Sept.) 1916.
14. Magnus-Levy: Deutsch. med. Wchnschr. **56**: 1150, 1919.
15. De Corral: Ztschr. f. Biol. **58**: 395, 1918.

Digitized by Google

This research, not yet confirmed, offers the only hint of which I am aware that the islet cells may be governed by nerves.

Nervous control of ductless glands involves the idea that they, like other structures governed by nerves, have their activities adapted to the needs of the body at different times. That the organism survives and lives normally when nerves to the suprarenal [16] or thyroid [17] gland are severed is not proof that the nerves are useless, any more than the continued service of the denervated heart as a pump is proof that the vagus and accelerator nerves are useless. The nerves may have, in relation to the glands, just as in relation to the heart, a tonic action for routine purposes; and at times of critical need they may have a special, or what I have called an "emergency" function, capable of rapidly mobilizing the bodily forces, internal secretions included, for the welfare of the organism as a whole.

No better illustration could be given of the tendency to regard the internal secretions as supreme and the nervous system as quite subordinate than in the theory underlying the clinical conceptions of vagotonia and sympathicotonia. Indeed, Eppinger and Hess,[18] the authors of the theory, have concluded that "the entire vegetative nervous system is under the control of the glands of internal secretion." Epinephrin is, indeed, able to reproduce almost all the changes that occur when sympathetic impulses are discharged. It has been supposed, therefore, to exercise a tonic action on sympathetic endings. For example, the height of arterial pressure is assumed to depend on the constant discharge of epinephrin into the blood stream, and a low blood pressure is ascribed to "hypo-adrenia." In order to have an antagonist for epinephrin—some sub-

16. Stewart, G. N., and Rogoff, J. M.: J. Pharmacol. & Exper. Therap. **10**: 1 (July) 1917.
17. Manley and Marine: Proc. Soc. Exper. Biol. & Med. **12**: 202, 1915.
18. Eppinger and Hess: Vagotonia, English translation, New York, 1915, p. 9.

Digitized by Google

stance which would take command of the opposing forces—Eppinger and Hess have conjured up a hypothetic hormone, "autonomin," acting like pilocarpin and physostigmin on the nerve endings of the cranial division of the automatic system. This assumed entity, first predicated in 1910, has never had the fortune of a real existence. Nevertheless, clinical literature has been rife with descriptions of cases with vagotonic and sympathicotonic dispositions.

It is well to recognize that there is no good evidence that epinephrin has any tonic effect in maintaining blood pressure. Aub [19] has measured the pressure four or five days after removal of both suprarenal glands and found it normal. Since epinephrin disappears from the blood a few minutes after it is injected or secreted, the continued normal pressure cannot be due to persistence of that substance in the blood. Stewart and Rogoff [16] have severed the nerves to one suprarenal gland and removed the other. Practically no demonstrable amount of epinephrin is secreted under such circumstances, and yet the animals remained for months in quite good condition. Gley and Quinquaud [20] have shown that vascular reflexes occur fully as effectively with the suprarenal glands absent as they do when the glands are present. Furthermore, Hoskins and McClure [21] pointed out, years ago, that an amount of epinephrin required to cause a rise of blood pressure is sufficient to stop all motions of the stomach and intestine. A ridiculous mechanism it would be that would stop digestion in order to provide a few extra millimeters of arterial tension! There is no satisfactory evidence that, in natural quiet existence, the suprarenal medulla gives off any secretion whatever. In times of stress it is brought into action by nerve

19. Aub: Am. J. Physiol., to be published.
20. Gley and Quinquaud: J. de physiol. et de path. gén. **17**: 807, 1918.
21. Hoskins, R. G., and McClure, C. W.: The Adrenal Glands and Blood Pressure, Arch. Int. Med. **10**: 343 (Oct.) 1912.

Digitized by Google

impulses and may, indeed, then support the influence of the sympathetic system, and have besides special functions of its own.[22]

The general arrangement of the sympathetic division is favorable to diffuse and widespread action in which a distributed chemical agent could participate. The vagus endings and the endings of the other parts of the cranial autonomic division lie in or near the organs innervated, and are therefore favorable to separate and discriminating action. By means of the general diffuse action of the sympathetic, and the opposite particular action of the parts of the cranial autonomic supply, every variety of change is provided for. All the viscera can be affected simultaneously in one way or the other through increased or decreased tone of the sympathetic division. And any special organ can be separately affected one way or the other through increased or decreased tone in the special nerve of the opposed cranial division that is supplied directly to the organ. The sympathetic is like the soft and loud pedals, modulating all the notes together; the cranial autonomic is like the separate keys.

A dilated pupil, for example, due to increased sympathetic activity attending excitement, should be accompanied by a rapid heart rate, vasoconstriction, stoppage of the motions of the stomach and intestine, and other evidences of widespread sympathetic influences. Epinephrin secreted at the same time would act synergistically with the nerve impulses. On the other hand, constriction of the iris by action of the motor oculi when the light is strong may not be accompanied by disturbance of any other part of the cranial autonomic supply to the viscera. Indeed, there is no conceivable advantage in having a mechanism in which strong light would result not only in a smaller pupil, but also in a slower heart rate and an increased tone of

22. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, New York, 1915, p. 184.

Digitized by Google

the gastro-intestinal tract. As one can readily perceive, a single substance, "autonomin," acting extensively, like pilocarpin, on cranial autonomic endings, might have most disorderly effects in forcing to operate coincidently and in an unadapted manner organs whose functions in calm existence are not importantly related to one another.

The ill-based theory of vagotonia has almost no respectable evidence to support it. Not only the criticism of laboratory workers but also the testimony of clinical observers has done much to discredit it. Cases are cited in which patients are equally hypersensitive to epinephrin and pilocarpin,[23] in which pilocarpin, atropin and epinephrin produce practically identical effects on the blood,[24] in which both atropin and epinephrin will stop auricular fibrillation,[25] and in which careful studies on various bodily functions showed no consistent sensitization to either the "sympathicotonic" or the "vagotonic" drugs. In the presence of the foregoing evidence, "vagotonia" becomes merely a name—a name which, as applied to the entire cranial autonomic division and presupposing a general reinforcing and vagotonic hormone, is wholly without meaning.

Reference was made above to the fact that activity of the sympathetic system may be varied up or down. Strong stimulation of an afferent nerve will cause vasoconstriction and other indications of diffuse sympathetic discharge, including suprarenal secretion. On the other hand, stimulation of the central end of the depressor nerve will cause vasodilation and a checking of any suprarenal secretion which may be going on.[26] Quite possibly, therefore, conditions may exist in the body, characterized by either greater or less sympathetic tone than normal; but such states would not be

23. Lehmann: Berl. klin. Wchnschr. **56**: 772, 1919.
24. Friedbery: Deutsch. med. Wchnschr. **46**: 480, 1920.
25. Loeffler: Schweiz Arch. f. Neurol. u. Psychiat. **8**: 177, 1921.
26. Cannon, W. B., and Rapport, D.: Am. J. Physiol. **58**: 338 (Dec.) 1921.

Digitized by Google

determined by independent dominance of suprarenal secretion, for, as shown above, lack of any secretion at all does not lessen the efficacy of sympathetic impulses, and extra secretion is ordinarily dependent on the effect of nerve impulses. The condition of the nervous system, not of the suprarenal medulla, therefore, is of primary moment.

In the foregoing review, evidence has been adduced to show the subjection of certain endocrine glands to nervous government. This emphasis, however, should not be interpreted as implying an independent dominance of the nervous system, for it, like other systems, is conditioned in its activities. Again I wish to lay stress on the fact that the body is an organism, and that the parts collaborate and exercise mutual influences on one another.

EVIDENCE FOR HUMORAL CONTROL

Nerves have been described as present in other of the endocrine glands than those mentioned above—for example, in the anterior lobe of the pituitary body [27] and in the parathyroid bodies.[28] On the other hand, it is reported that no nerve fibers are distributed to the interstitial cells of the testis, and very few to the suprarenal cortex. Nevertheless, both these structures may undergo hyperplasia, associated, at least in the case of the interstitial tissue, with seasonal depression at times of sex activity.[29] Evidently some other mode of control besides nerve impulses must prevail in such conditions. And since the blood stream alone brings the glands into relation with other parts, it is naturally assumed that the influences affecting the glands and passing away from them are conveyed in the circulating blood. In other words, the influences are of the humoral type.

27. Berkeley: Brain **17**: 515, 1894.
28. Schäfer: The Endocrine Organs, London, 1916, p. 21.
29. Tandler and Grosz: Arch. f. Entwicklungsm. **33**: 297, 1911.

Digitized by Google

The presence of a nervous control of internal secretion does not preclude a humoral control. Thus, the heart and the stomach and intestine are readily influenced by nerve impulses. But they are likewise affected by epinephrin discharged by the suprarenals, i. e., by a humoral agent. Also the thyroid, though subject to nerve stimulation, is responsive to chemical factors brought by the blood. For example, Cattell and I [80] found some years ago that stimulation of a discharge from the suprarenal medulla would cause an electrical action current in the thyroid.

When we begin to consider the evidence for interrelation of the ductless glands, we find ourselves in a maze of complex possibilities, contradictory reports and uncertain inferences. Much of the evidence is derived from distant effects of ablation or destruction of one or more of the glands, or from changes due to tumor growth, or to feeding gland substance. None of these circumstances can be regarded as physiologic. The results may be suggestive of *some* relation between the gland removed, or abnormal, or fed, and the other gland or glands which are altered thereby. But it is hazardous to draw inferences from pathologic states relative to physiologic processes. And even if there is *some* relation, we have not made satisfactory progress until we know what the relation is, the way it works and its full significance. If we knew nothing of the function of the heart and as much as we now know about the endocrine organs, we might be led to infer that the semilunar valves exercise an inhibitory influence on the growth of the heart; for does not destruction or injury of the valves result in an enlargement of that organ? Do we reason any better than this in many of our inferences from the effects of experimental removal of the endocrine organs? We know almost nothing, for example, about the normal func-

30. Cannon, W. B., and Cattell, M.: Am. J. Physiol. **41**: 74 (July) 1916.

Digitized by Google

tioning of the suprarenal cortex. Several observers have confirmed Hoskins'[31] observation that feeding thyroid gland enlarges the suprarenal body, especially the cortical portion, according to Herring.[32] It is reported to be enlarged also by starvation[33] or by a diet deficient in vitamins.[34] And Gley[35] and also Carlson[36] have found enlargement of the suprarenal bodies after removing the thyroid glands. Is the enlargement due to stimulation by the thyroid, or is it compensatory to increased metabolism, or is it a biologic response conservative of important bodily material when the supply is low or is being rapidly consumed? These are some of the possibilities. Certainly, in the presence of these complexities one has no clear idea of thyroid influence on suprarenal function.

Possibly too much emphasis has been laid on mere changes of size. More than thirty years ago, Rogowitsch[37] first noted that thyroidectomy is followed by hypertrophy of the pituitary body. This observation has been confirmed by numerous investigators. Kamo,[38] who removed the thyroid from young dogs, found, after a few months, marked pituitary enlargement, even to more than twice the normal size, manifested chiefly in the anterior lobe. We commonly associate hypertrophy with extra activity, and we have evidence that extra activity of the anterior lobe of the pituitary body is attended by an overgrowth of the skeleton. Animals deprived of the thyroid, however, are stunted in growth. Here we have an instance of hypertrophic change in one gland induced by removal of another, but with no corresponding hyperfunctional effect.

31. Hoskins: Am. J. Physiol. **26**: 426, 1910.
32. Herring: Quart. J. Exper. Physiol. **11**: 47, 231, 1917.
33. Byrne, C. H. C.: Brit. M. Jour. **2**: 135 (Aug. 2) 1919.
34. McCarrison, R.: Brit. M. J. **2**: 236 (Aug. 14) 1920.
35. Gley: Arch. internat. de physiol. **14**: 175, 1914.
36. Carlson, A. J., in discussing Cannon, W. B.: Results of Recent Studies on Ductless Glands, J. A. M. A. **67**: 1483 (Nov. 18) 1916.
37. Rogowitsch: Beitr. z. path. Anat. u. z. allg. Path. **4**, 1889.
38. Kamo: Jap. Med. Lit. **3**: 33, 1918.

Digitized by Google

Perhaps we shall have clearer signs of the cooperation of the endocrine organs if we consider briefly the influence of various representative glands on a common function. For illustrative purposes I propose to call attention to some of the effects of the glands on certain bodily processes, which were mentioned earlier —growth, reproduction and metabolism.

The relation between overgrowth of the skeleton, as in gigantism and acromegaly, and hyperplasia of the anterior lobe of the pituitary, is now fairly well established. Extra skeletal growth is also associated with early castration. On the other hand, both clinical and experimental studies point to early pituitary deficiency as causing failure of bony development. This form of dwarfism is characterized by both short and slender bones. A third gland whose function is essential to growth is the thyroid, for in its absence the stature is stunted. Here are three endocrine organs, all having marked influence on the attainment of normal size. One could readily speculate as to how they influence one another—the pituitary and thyroid appearing to work cooperatively and the gonads acting as a check on them—but we need facts rather than speculation.

Reproduction depends on the gonads, of course, but it also depends on the thyroid and the pituitary glands. If the young animal is deprived of either the thyroid or the pituitary, the generative organs are only slowly or imperfectly developed, so that a condition of sexual infantilism persists. Hyperplasia of the pituitary, and also of the suprarenal cortex, in the young, is sometimes associated with precocious sexual maturity and activity. Both the thyroid and the suprarenal cortex become enlarged during pregnancy. Thus, the evidence seems to point to the thyroid and the pituitary glands and to the suprarenal cortex as factors essential to proper establishment of the reproductive function, and also possibly collaborating, in the female, in the performance of that function.

Digitized by Google

The pancreas, the suprarenals and the liver primarily, and likewise the thyroid and the pituitary, are all concerned with carbohydrate metabolism. As is well known, excision of the pancreas results in diabetes, stimulation of the liver or injection of epinephrin increases the sugar in the blood, and removal of either the thyroid or the pituitary raises the assimilation limit of sugar. Diabetes is occasionally associated with acromegaly and with exophthalmic goiter. Probably all five of the glands mentioned above either cooperate or form a fairly stable combination of opposed influences. But, again, how these organs are interrelated in their effects on metabolic processes is not at all clear.

In the foregoing paragraphs I have merely hinted at some of the signs of cooperation among certain endocrine glands. My purpose in doing so was to make the point that here, just as in the nervous government of internal secretion, there are indications that we are dealing with arrangements which are normally well ordered and subject to automatic control. Bodily functions are managed by a system of checks and balances—by mutual adjustments such as those between antagonistic muscles, and by maintained equilibria, such as those between material income and outgo, and between acid and base in the blood. We are justified by what we already know of bodily organization in looking for similar modes of restraining and releasing the internal secretions. If the endocrine glands are regarded as the regulators of important physiologic processes, normally they are well regulated regulators. Much work must still be done, however, before we shall know the mechanisms whereby the control of these agents is exercised. But the work is highly important because of the potency of the endocrine organs when they are deficient or when they escape control and through pathologic activity play havoc with our internal adjustments.

Digitized by Google

THE RELATION OF THE INTERNAL SECRETIONS TO METABOLISM *

JOSEPH C. AUB, M.D.
BOSTON

Among the various functions ascribed to the glands of internal secretion, the regulation of metabolism ranks high. Not only is it a very important part of their activity, but it is also the function about which the greatest and most accurate knowledge has been accumulated. Of course, the general regulation of metabolism is not wholly controlled by the glands of internal secretion, for there are many other factors which exert influences which cannot now be ascribed to the activity of these glands. Examples are found in the effect of exercise, the specific dynamic action of foodstuffs, fasting, sleep, etc., and it therefore cannot be assumed that these endocrine glands absolutely control the rate of metabolism. But there can be no doubt that their general influence is great.

As far as our knowledge goes, this influence is largely exercised on the heat production as a whole rather than on individual components of metabolism, such as the carbohydrates or salt. This is not true of all of the glands. The pancreas has a differential action and exerts its regulatory effect largely upon the utilization of carbohydrate. It is also possible that the parathyroids have some isolated influence on the metabolism of inorganic salts.[1] It is also true that the metabolic effects of other glands may be developed predominantly from one foodstuff, as in the combustion of carbohydrate after the administration of epi-

* From the Laboratories of Physiology of the Harvard University School of Medicine.

1. Boothby, W. M.: The Parathyroid Glands, Endocrinology 5: 403-440, 1921.

Digitized by Google

nephrin;[2] but, in general, apart from the action of the pancreas and the parathyroids, the effect on the total rate is a fairly good index of the general influence of the glands on the body metabolism, at least as far as we know.

The effect of each gland on the metabolic rate has been the subject of considerable recent investigation, so that a short summary of the work is difficult. It is probably true that many glands credited with various effects produce these effects by indirect reactions on other glands, so that they are really merely indications of interrelationships. The problem of interrelationships among these endocrine glands is difficult and should be discussed only when based on careful experimental data. It is with this point of view in mind that I shall undertake, first, to show that probably only two glands, the thyroid and the suprarenals, are fundamentally and chiefly involved in the regulation of the total metabolic equilibrium; and, second, to suggest the mechanism of their action as fully as present knowledge will permit.

A summary of the literature discloses the fact that there are four glands to which are attributed an influence on the rate of metabolism.[3] Of these, the thyroid gland stands preeminent, and its stimulating action is so well known that further discussion is not essential here. The gonads are also a factor, although a minor one. Their removal is followed, after a period of about three weeks, by a fall in metabolism, as has been shown by Loewy and Richter,[4] Luethje,[5] Murlin [6] and others.

2. Boothby, W. M. ,and Sandiford, I.: The Relationship of the Increase in Blood Sugar Concentration to the Specific Dynamic Action of Glucose and to the Specific Dynamic Action of Adrenalin, Am. J. Physiol. **55**: 293-294, 1921.

3. Aub, J. C., and Taylor, M.: The Effect of Body Tissues Other Than the Thyroid upon the Basal Metabolic Rate, Endocrinology, to be published.

4. Loewy, A., and Richter, P. F.: Sexual Function und Stoffwechsel: Ein experimenteller Beitrag zur Frage des Einfluss der Organotherapie, Arch. f. Physiol., Suppl., 1899, pp. 174-198. Zur Frage nach den Einfluss der Castration auf den Stoffwechsel, Centralbl. f. Physiol. **16**: 449-452, 1902.

5. Luethje, H.: Ueber die Castration und ihre Folgen, Arch. f. exper. Path. u. Pharmakol. **48**: 184-222, 1902.

6. Murlin, J. R., and Bailey, H.: The Relations of the Sex Glands to Metabolism, Surg., Gynec. & Obst. **25**: 332-336, 1917.

Digitized by Google

Korenchevski,[7] taking the data of his pupil Rovinski,[8] showed that this fall of metabolism after castration largely disappeared if the thyroid gland was first removed. He therefore concluded that the effect of the gonads on metabolism was accomplished through an interrelation with the thyroid gland, and that the lowered metabolism following castration was due to a depression of thyroid secretion rather than directly to absence of the gonads.

The influence exerted by the anterior pituitary is similar to that of the gonads, in that, after extirpation, there is a gradual reduction of the basal metabolic rate. This was first shown by Benedict and Homans.[9] Sometimes one finds, clinically, changes in the rate of metabolism of patients with active disease of the pituitary; but this is not a constant finding. Boothby has recently stated (at the Society of Clinical Investigation) that, in his experience, these changes in acromegalias were always found in those patients who also showed some thyroid involvement. It is therefore possible, although it has not been finally proved, that the metabolic effects of the pituitary are accomplished through the thyroid just as, probably, in the case of the gonads. Administration of the glandular products of these two, however, has not affected the metabolism consistently, and further work needs to be done along these lines.

The fourth organ which regulates the metabolism is the suprarenal. This is a recent discovery. Most of the work on this subject has been of a pharmacologic nature, by the subcutaneous and intravenous injection of large doses of epinephrin, as in the experiments of

7. Korenchevski, V. G.: Die Beziehungen zwischen Schild- und Keimdrüsen in Verbindung mit deren Einfluss auf den Stoffwechsel, Ztschr. f. exper. Path. u. Therap. **16**: 68-69, 1914.

8. Rovinski, M. I.: The Influence of Thyroidectomy and Castration upon the Gaseous and Nitrogenous Interchange of Substances in Animals (Russian), Dissertation, Petrograd, 1913.

9. Benedict, F. G., and Homans, J.: The Metabolism of the Hypophysectomized Dog, J. M. Res. **25** (n. s 20): 409-502, 1912.

Digitized by Google

Tompkins, Sturgis and Wearn,[10] Sandiford[11] and others. Their results have shown that there is an invariable rise of metabolism, which develops and disappears within a period of minutes. Boothby and Sandiford showed that this could not be explained by a mere mobilization of glucose.[2] These pharmacologic observations suggested that the secretions of the suprarenal glands, as they occur physiologically, might play a rôle in the regulation of metabolism; and Miss Bright, Dr. Forman, Dr. Uridil and I[12] have studied this possibility. We found that removal under ether anesthesia of the suprarenal glands of cats was followed by a rapid reduction of the metabolic rate. This occurred while the animal was still in good condition, and persisted until the final collapse.

At the meeting at which these experiments were reported, Marine[13] announced his results with rabbits: he laid stress on a belated and temporary increase in metabolism, which he has subsequently[14] interpreted as due to secondary thyroid activity. We have not investigated the transient rise in metabolism which he reports; but we have studied the fall of metabolism obtained so definitely in cats. It was found that if the suprarenal glands were removed under urethane anesthesia, the fall in metabolism appeared shortly and tended to progress. In these experiments, the cat remained in an anesthetized condition throughout the entire observation. The observed fall in metabolism was not affected by injections of extracts of the supra-

10. Tompkins, E. H.; Sturgis, C. C., and Wearn, J. T.: The Effects of Epinephrin on the Basal Metabolism in Soldiers with "Irritable Heart," in Hyperthyroidism, and in Normal Men, Arch. Int. Med. **24**: 269-283 (Sept.) 1919.

11. Sandiford, I.: The Effect of Subcutaneous Injection of Adrenalin Chloride on the Heat Production, Blood Pressure, and Pulse Rate in Man, Am. J. Physiol. **51**: 407-422, 1920.

12. A Full Report of These Experiments Will Appear Shortly in the American Journal of Physiology.

13. Marine, David, and Baumann, E. J.: The Influence of Glands with Internal Secretion on the Respiratory Exchange, II, Effect of Suprarenal Insufficiency (by Removal or by Freezing) in Rabbits, Am. J. Physiol. **57**: 135-152, 1921.

14. Marine, David, and Baumann, E. J.: Influence of Glands with Internal Secretion on the Respiratory Exchange, III, Effect of Suprarenal Insufficiency in Thyroidectomized Rabbits, Am. J. Physiol. **59**: 353-368, 1922.

Digitized by Google

renal cortex, but could be eliminated by intravenous injection of epinephrin administered at a rate which is said to be physiologically probable in life, according to Stewart and Rogoff,[15] and Cannon.[16] This has recently been confirmed by Boothby and Sandiford[17] in the dog with intact suprarenals. Such results are certainly good evidence that the suprarenal glands may play a part in the variation of the metabolic rate by means of the normal secretion of epinephrin. Clinical evidence for this is not so readily found, but it is probably seen in the high metabolic rates often found in the first observations made on excited patients. It is not rare to find an untrained nervous subject who is emotionally disturbed by the procedure of the test. Such patients may then show a higher metabolic rate than they display later, even though they remain quiet. According to the emergency theory of Cannon,[18] it is during such excitement that epinephrin would be secreted. In the few cases of Addison's disease reported with metabolic studies, evidence of reduced metabolism has been shown either by the nitrogen elimination or by the basal metabolic rate; but these cases are still too few to generalize about.

Are the metabolic effects of thyroxin and epinephrin independent? Marine[19] has shown that the increase of metabolism which follows the injection of epinephrin may be obtained in animals which have been previously deprived of their thyroid glands. Similarly, we have shown that the reduced metabolic rate following

15. Stewart, G. N., and Rogoff, J. M.: Quantitative Experiments on the Liberation of Epinephrin from the Adrenals after Section of Their Nerves, with Special Reference to the Question of the Indispensability of Epinephrin for the Organism, J. Pharmacol. & Exper. Therap. **10**: 1-48 (compare p. 3), 1917.

16. Cannon, W. B., and Rapport, D.: Studies on the Conditions of Activity in Endocrine Glands, VI, Further Observations on the Denervated Heart in Relation to Adrenal Secretion, Am. J. Physiol. **58**: 308-337, 1921.

17. Boothby, W. M., and Sandiford, I.: Calorigenic Effect of Adrenalin in Dogs, Am. J. Physiol. **59**: 463-464, 1922.

18. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, New York, D. Appleton & Co., 1915.

19. Marine, David, and Lenhart, C. H.: The Influence of Glands with Internal Secretion on the Respiratory Exchange, I, Effect of the Subcutaneous Injection of Adrenalin on Normal and Thyroidectomized Rabbits, Am. J. Physiol. **54**: 248-260, 1920.

Digitized by Google

suprarenalectomy under urethane and the stimulating effects of epinephrin when it is injected at a physiologic rate are demonstrable in animals either with or without the thyroid gland. It is therefore clear that the thyroid gland is not an essential factor in the action of epinephrin on metabolism. That the converse of this is true, that the suprarenal glands are not essential for the continued stimulation of metabolism by thyroxin, may be shown in the following manner: The metabolic rate is raised above normal by the injection of thyroxin. If the suprarenal glands are now removed, the metabolic rate does not fall to normal but is maintained at a high level for many hours, so that the high metabolic rate in hyperthyroidism is not dependent on the presence of the suprarenal gland or its secretions. It is therefore fair to assume that the calorigenetic effects of thyroxin and epinephrin are distinct and not interdependent. The time relations of their actions also differ distinctly. Studies at the Mayo Clinic first revealed that the metabolic effects of the injection of thyroxin are manifest only after many hours and last for days. Epinephrin, on the contrary, produces effects within minutes, not hours, and likewise loses its influence after a brief period. All these facts have led me to the theory that there is a double endocrine mechanism for regulating the metabolic rate; that some of the acute fluctuations of basal metabolism may be ascribed to the influence of the suprarenal glands, and that the thyroid is more sluggish, but probably more important in its regulatory action.[12] Such a mechanism would be analogous to the control of the acid-base equilibrium of the blood, as demonstrated by L. J. Henderson, in which the lungs and kidneys share the burden, the lungs making the necessary immediate adjustments by the excretion of carbon dioxid, the kidneys, acting more sluggishly, by the excretion of phosphates.

What is known about the way in which these hormones accomplish their metabolic effects? This is a field in which further investigation is needed. Most work has been directed to determining the nature of

Digitized by Google

the metabolic effects rather than to determining how they are accomplished. But we do know some facts. Thus it has been found by Lovatt Evans [20] that epinephrin will stimulate the isolated heart to more rapid contractions and to a markedly increased metabolism. Recently, Martin and Armitstead have shown [21] that an isolated resting muscle has a higher metabolism, as denoted by acid production, when in the presence of epinephrin than when no epinephrin is present. These two experiments point to the action of epinephrin as a direct one, capable of influencing metabolism by affecting peripheral muscle tissue directly, as Boothby suggested. There is apparently no need of the central nervous system or of other internal secretions as accessories to its stimulating action, but it must work as a direct metabolic stimulant either on the nerve end plates or on the muscle cells themselves.

No such clear evidence exists, however, in support of the theory that the thyroid acts on cells by stimulating them directly to increased heat production. It is, of course, a more difficult problem because there is so long a latent period before thyroxin manifests its effects, so that no rapid experiments can be made. One might determine the metabolism of an isolated muscle, then make the animal thyrotoxic and determine the metabolism of the opposite corresponding muscle. This has not yet been done, so far as I know, so that the actual method by which the thyroid secretion stimulates metabolism is not yet known.

The acute effects of a thyroid preparation on the isolated heart were studied by Richardson,[22] and later by Kakehi [22] in Asher's laboratory. They could see no

20. Evans, C. L., and Ogawa, S.: The Effect of Adrenalin on the Gaseous Metabolism of the Isolated Mammalian Heart, J. Physiol. **47**: 446-459, 1914.

21. Martin, E. G., and Armitstead, R. B.: The Influence of Adrenalin on Metabolism in Isolated Skeletal Muscle, Am. J. Physiol. **59**: 37-43, 1922.

22. Richardson, H. B.: Beiträge zur Physiologie der Drüsen, XXIV, Wirkung innerer Sekrete, insbesondere von Schilddrüsensekret und Adrenalin, auf das überlebende Säugetierherz, Ztschr. f. Biol. **67**: 57-82, 1916. Kakehi, S.: Beiträge zur Physiologie der Drüsen, XXV, Fortgesetzte Untersuchungen über die Wirkungsweise von Schilddrüsensekret auf das überlebende Herz von normalen und schilddrüsenlosen Tieren, ibid. **67**: 104, 1916.

Digitized by Google

prompt effect from the presence of the thyroid alone on either the amplitude or the rate of the heart beat, but they did not study the metabolism. It is probable that no immediate effect would be elicited, however, because of the latent period in the metabolic action of the thyroid. Therefore, the theory of the general action of thyroxin directly on cells still needs an experimental basis. We have, however, been able to study the metabolic effects of hyperthyroidism, particularly in regard to the rôles played by activity, tremor and muscle tonus.

Marie Krogh,[23] in a preliminary report published some years ago, suggested that muscle tonus might be the factor in the increased metabolism, and many have often thought, I am sure, that the stiking evidences of muscular activity might explain the high metabolism in thyroid disease. We studied animals rendered thyrotoxic by the injection of thyroxin. Their metabolism rose in a few days to a level usually more than 50 per cent. above their previous basal values. When urethane anesthesia was then induced, and the metabolic rate again determined, it was found that the level remained high in spite of the fact that there was no muscle tremor and no activity other than cardiorespiratory movements. If now the nerves to the limbs were cut, the possibility of any tonus arising from either myelinated or sympathetic nerves was practically eliminated. Even this procedure did not cause the metabolism to return to its original level. It is therefore quite clear that neither activity nor muscle tremors nor muscle tonus explains the high metabolism found in hyperthyroidism.

To show how fundamental are the metabolic effects of these two internal secretions, it is interesting to note, here, that they may still be found under urethane anesthesia, although the metabolic stimulation from caffein or amino-acids has then disappeared.[24] What

23. Krogh, Marie: The Influence of Thyroidin on Normal Metabolism, Ugesk. f. Læger **78**: 2337-2340, 1916.
24. Aub, J. C.; Everett, M. R., and Fine, J.: Unpublished data.

Digitized by Google

the significance of this difference is, however, cannot be analyzed at present. And so we return to the conclusion, often suggested, that the effects of both epinephrin and thyroxin on the metabolism are probably similar to that of increasing the draft under a fire. This is fairly clearly established for epinephrin, but needs further evidence for the action of thyroxin. It is true that the evidence brought forward in this paper has related largely to the two active substances which have been isolated from the thyroid and the suprarenals. They probably have at least one more secretion: that derived from the suprarenal cortex. Extracts from it have had no acute effects on metabolism in our hands, and its function remains mysterious, although essential to life. Whether it, too, has a metabolic function remains to be proved.

CONCLUSIONS

1. Apparently, the two glands which most influence the total metabolism are the thyroid and the suprarenal (probably by epinephrin).

2. The mechanism of their actions are independent. Collected evidence shows that the calorigenetic action of thyroxin is manifest without the suprarenals; that of epinephrin is present without the thyroids.

3. The theory is advanced that the suprarenals exert acute effects, while the thyroid is the more sluggish regulator of the metabolic rate.

4. The method of action of thyroxin and epinephrin on the body tissues has been discussed.

Digitized by Google

HYPOFUNCTION AND HYPERFUNCTION OF THE DUCTLESS GLANDS

A. J. CARLSON PH.D., M.D.
CHICAGO

It is difficult, if not impossible, to present the subject of endocrine dysfunction in a brief article, without appearing to be both ignorant and dogmatic; ignorant of many alleged facts, because time does not permit giving the reasons for their rejection, and dogmatic because practically every statement made in regard to the ductless glands today requires qualification, which is, for the most part, ruled out by the time limit. Furthermore, I take part in this discussion with the diffidence of a man whose personal experience is limited largely to the experimental side of the subject. However, I have a fair acquaintance with the entire endocrine literature, in both the field of science and the field of fiction, and I take for granted that we all subscribe to the principle that the rules of evidence or criteria for facts are the same in the experimental and in the clinical fields.

HYPOFUNCTION

When the ductless glands are so situated that they can be surgically extirpated, in whole or in part, without injury to important adjacent organs, the extirpation of these glands in the healthy animal gives us the most reliable information regarding the results of hypofunction of each specific system. The hypofunction syndrome may be complex and may gradually involve endocrine organs other than those extirpated, but the initial cause can with certainty be referred to absence of the function normally carried out by the organ which has been removed. This ideal anatomic condition obtains in the case of the thyroids, the parathy-

Digitized by Google

roids, the pancreas, the thymus, the ovaries and the testes. In most animals, the cortex and medulla of the suprarenal glands are so closely fused that it is difficult to extirpate the one without grave injury to the other. This applies also to the two (or three) systems that make up the pituitary gland. Furthermore, the location of the pituitary and the pineal glands within the cranial cavity and close to the midbrain renders it difficult to extirpate these organs without injury to the base of the brain, and tumors or cysts in these glands practically always involve brain injury by pressure.

Extirpation experiments in healthy animals have thus established the following general facts:

Loss of the thyroid is followed by cretinism in the young and myxedema in the adult. But it should be noted that some of the myxedema symptoms following hypothyroidism in man are not readily produced even by complete thyroidectomy in the healthy adult animal.

Loss of the parathyroids induces depression, tetany and death in a few days, unless the animal is subjected to special dietary and diuretic control.

Loss of the pancreas leads to absolute diabetes and death from diabetes (in the dog) in from four to seven weeks.

Loss of the testes is followed by persistent sexual infantilism in the young, and in the adult by loss of the sex urge and sex functions, and by gradual atrophy of most of the secondary sex characters.

Loss of the ovaries results in persistent sex infantilism in the young and in premature menopause and gradual atrophy of most of the secondary sex characters in the adult.

Loss of the suprarenal medulla induces no symptoms and no disease, according to the most reliable observations.

Loss of the suprarenal cortex causes profound prostration and death within a few days, in what appears to be acute Addison's disease.

Digitized by Google

Loss of the posterior lobe of the pituitary gland appears to produce no definite symptoms. There are competent investigators claiming that this lesion induces diabetes insipidus and disturbance of metabolism, while equally good workers hold that diabetes insipidus is caused by injuries to the base of the brain outside the hypophysis. The question is not settled.

Loss of the anterior lobe of the pituitary gland appears to produce impairment of growth and infantilism in the young, and in the adult a tendency to adiposity and somnolence, with atrophy of the gonads and failure of sex functions. According to one group of investigators, complete extirpation of the anterior lobe leads to death, in profound depression, in a few days; while another group of equally competent men claim that such deaths are due, not to the loss of the gland, but to injury to the base of the brain. This question is open. But all workers are agreed that almost complete loss of the anterior lobe (including unavoidable injuries to the base of the brain) leads to hypopituitary infantilism, at least in a percentage of the animals so operated on.

Extirpation of the pineal gland causes no symptoms. The loss of the spleen or the duodenum is also without endocrine effects. Extirpation of the thymus produces no effect, except perhaps slight hastening of adolescence in the young.

Time does not permit a further analysis of the hypofunction syndromes just outlined. The hypothyroid and the hypopituitary syndromes are particularly difficult to evaluate or diagnose because of the variability of some of their major elements. We must, therefore, clearly recognize that while the terms cretinism, myxedema or hypopituitary infantilism are permissible and useful in relation to primary etiology, these terms cannot be used as formulas representing facts established, and hence as a certain basis for therapy. A cynical judge once asked, "What is truth?" but did

Digitized by Google

not tarry for an answer. The question, What is hypothyroidism or hypopituitarism may be laughed out of court as "academic," or as already settled by this audience of "practical men"; but I raise it nevertheless as a challenge to those who would sacrifice honesty for short cuts to commercial success, and those who would practice the trade of the quack under the protecting cloak of membership in an honorable profession.

These extirpation experiments on healthy animals, from embryos to adults, permit the following generalizations:

1. Each system of ductless glands appears to be essentially identical in function in all classes of vertebrates. This fact renders it highly probable that corresponding glandular hypofunctions in man will induce similar syndromes. We know that this is the case in regard to the gonads, from the effects of gonadectomy in healthy men and women.

2. None of the ductless glands appear to work to full capacity under normal conditions, since from three quarters to seven eighths of each gland system may be removed in the healthy animal without producing any deficiency symptoms. This is a very disturbing factor in the clinical field when we attempt to relate the histopathology of the ductless glands to the patient's disease.

3. No matter what changes in the way of atrophy or hypertrophy may be induced in the remaining ductless glands on extirpation of any one gland system, the essential effects following distinct hypofunction of each gland system appears to be specific for that system. In other words, extirpation experiments on healthy animals afford little or no evidence of substitution or vicarious functioning by the ductless glands that remain in the animal.

4. The symptoms produced by the extirpation of the ductless glands in healthy animals can be inter-

Digitized by Google

preted either on the hormone theory or on the detoxication theory.

5. No chemical methods are at present available by which we can demonstrate the presence of hormones and their quantitative variations in the blood and tissues, or even in the glands themselves. The iodin in the thyroid appears to be somewhat of an index of the thyroid secretion. We can make iodin determinations of the blood, the lymph, and the other tissues of the body, but we cannot conclude that the iodin found represents thyroidin and this only. We have chemical tests for epinephrin, but epinephrin is probably not a hormone.

In regard to the possibility that some, if not all, of the ductless glands may work on the principle of detoxication, it is equally true that we have no chemical tests for the toxins in the blood and tissues that may be responsible for the hypofunction syndromes, except possibly in the case of the parathyroids. Recent work seems to demonstrate that the tetany and death following extirpation of the parathyroids are due to toxic protein derivatives produced by the action of the colon group of organisms on the animal proteins of the food. Some of these toxic protein derivatives can be chemically isolated. The foregoing facts may be stated positively by saying that, so far, the tests for hypofunction of the ductless glands are indirect or biologic.

6. The relative immunity of some individuals to complete or nearly complete extirpation of some of the ductless glands is usually explained by the age factor (the young being less immune) and by abberrant or accessory glandules. That accessory glandules of some of the systems frequently occur is well known, but we question the adequacy of these explanations for all the exceptions.

In the clinical field, results fairly comparable to those following extirpation of endocrine systems in

Digitized by Google

healthy animals are produced by clearly destructive lesions in single gland systems. Such lesions as tuberculosis, cystic degeneration, fibrosis, or atrophy, when including all or nearly all of the glands, are practically equivalent to extirpation with the knife, provided the lesions are strictly localized. Such strict limitations of destructive lesions are rarely found in postmortems, especially in persons past from 30 to 40 years; but when they are established, we have what may be called frank hypofunction, and the etiology of the syndrome is just as clear as in total or partial extirpation of a one gland system in healthy animals. In this way, the combination of careful clinical observations and postmortem studies have proved that hypothyroidosis and athyroidosis lead to cretinism and myxedema; that total or nearly total destruction of the suprarenal cortex leads to Addison's disease and death; that sufficient cystic degeneration of the hypophysis is followed by infantilism, and that marked destruction of the pancreas induces diabetes. Castration and spaying produces the same effects in man as in experimental animals, with the additional factors of nervous disturbances of the menopause and, probably, in some males, purely subjective effects in the way of feelings of regret or melancholia.

There is no reliable evidence that hypofunction of the suprarenal medulla induces deficiency symptoms. The theory of "suprarenalemia" as a clinical entity or disease is an illustration of where mere logic may lead us, when the major premise is an error.

The foregoing clinical conditions may be designated as frank hypofunctions of the ductless glands; and when the gland lesions approach complete destruction or atrophy, diagnosis can usually be made with a fair degree of certainty. I make this statement with a good deal of hesitation, particularly in connection with the thyroid and the hypophysis. Most of us have accepted as demonstrated facts the view that the thy-

Digitized by Google

roid secretion has a direct stimulating action on the basal metabolism, and that increase or decrease of the thyroid secretion in the body can be demonstrated by changes in the metabolic rate, at least as early and as clearly as any of the other changes in body functions that are supposed to be due to quantitative changes in the thyroid secretion. But now come apparently reliable clinical reports to the effect that: (1) so-called hyperthyroidism or toxic goiter may be present with a normal metabolic rate, and (2) hypothyroidism or myxedema may be present and parallel with a high, a low or a normal basal metabolism. If these are facts, it is clear that the present basal conceptions of thyroid physiology must be revised. But first let us make sure that these new observations are really facts. And, in the meantime, let us be still more careful in the diagnosis of clinical hypothyroidism and hyperthyroidism.

If our foundation is so shaky in clinical cases of what appears to be frank hypofunction of the ductless glands, what can we expect in only slight degrees of hypofunction? Here we have no aid from the macroscopic and microscopic conditions or chemical analysis of the glands, as such conditions are chronic rather than speedily fatal; and even when the glands or part of a gland is available for study, the interpretation of the histologic findings is mostly conjecture.

The other serious difficulty in the recognition of slight degrees of endocrine hypofunction is the fact that, in the case of some of the endocrine systems, the hypofunction must be considerable before the syndrome becomes clearly specific. This applies particularly to most of the nervous manifestations of endocrine hypofunction. Slight nervous disorders, slight gastro-intestinal disorders, slight disorders of metabolism, slight disorders of the sex life, seem to be produced by conditions in which evidence for primary endocrine etiology is lacking.

Digitized by Google

ALLEGED ENDOCRINE HYPERFUNCTION

The question of endocrine hyperfunction is not of as great importance in medicine as that of hypofunction, in view of our present knowledge. Hyperfunction must, of course, be considered in connection with the alternative theory of dysfunction or toxic secretion. The question of hyperfunction has no meaning or application in glands that work by detoxication.

1. Spontaneous endocrine hyperfunction is unknown in experimental animals. Much work has been done in the attempt to produce experimental hyperthyroidism in animals by thyroid feeding. Large doses of thyroid extract produce some of the symptoms of toxic goiter, such as increased metabolism, tachycardia, emaciation and gastro-intestinal disturbances. The nervous and ocular manifestations of toxic goiter are not produced.

2. In man, endocrine hyperfunction is assumed by many people as a causative factor in:

(1) Toxic goiter (the thyroids); (2) acromegaly (the hypophysis, anterior lobe); (3) hypertension (the suprarenal medulla and the thyroids); (4) precocious puberty (the suprarenal cortex, the hypophysis and the pineal gland); (5) diabetes (the thyroid); (6) excessive sex urge (the gonads); (7) excessive menstruation (the ovaries or the corpus luteum).

Now, what are the facts? In the first place, mere increase in the size of glands, mere hyperplasia, does not mean more gland activity or more secretion. We have thyroid hyperplasia and thyroid adenomas without physiologic disturbances, yet the size, structure and chemistry of the thyroid appear identical to these facts in toxic goiter. Biologic and chemical tests of the blood at present are not delicate enough to detect the thyroid secretion or quantitative variations of the secretion. The colloid and iodin of the thyroid is usually reduced in toxic goiter, but this is also the case in thyroid hyperplasia associated with no toxic symptoms.

Digitized by Google

Furthermore, the reduced quantity of iodin, thyroglobulin or thyroxin in the gland may mean that the gland is producing more secretion; it may also mean that the gland produces less secretion. It is a fact that excessive thyroid feeding induces in man some of the symptoms of toxic goiter. Apart from this, the results of medical and surgical management of toxic goiter can be equally well explained on the basis of a toxic or perverted secretion. This theory, moreover, is not inconsistent with the existence of myxedema and toxic goiter symptoms in one person at the same time. This condition is difficult, if not impossible, to explain on the theory of hypersecretion. The primary relation of exophthalmic goiter to the thyroid may not be cleared up until complete thyroidectomy is made in a well controlled series of patients having toxic goiter. I believe this can be done without harm to the patient, if one or two parathyroids are spared or the parathyroprival symptoms are controlled by diet and diuresis, and possible myxedema controlled by thyroid feeding. There are plenty of patients with toxic goiter showing little or no improvement on either surgical, roentgen-ray or medical therapy. Such patients would probably be better off with some myxedema than with severe exophthalmic goiter, and the medical profession would have taken a step forward through knowing with certainty the primary relation of the thyroid to toxic goiter.

We encounter similar difficulties in the relation of pituitary hyperplasias and tumors to acromegaly. We know for a fact that hypophysial adenomas or hyperplasias are associated with acromegaly, just as thyroid hyperplasias are associated with exophthalmic goiter. But the causal connection between the gland enlargement and the disease is obscured by the fact that we have hypophysial hyperplasias and tumors with acromegaly, and acromegaly without tumors of the hypophysis. Nothing resembling acromegaly has so far

Digitized by Google

been produced experimentally by administration of hypophysial preparations. And the final difficulty is the condition of unilateral acromegaly, a fact that appears irreconcilable with the simple excess hormone theory of causation.

We may now ask whether any of the disorders of the sex life have been found to be due to hyperfunction of the gonads? If we could uncover the processes of life by logic alone, we might conclude that, since gonadectomy or frank gonad hypofunction decreases or abolishes nearly all manifestations of sex, excessive manifestation of the sex urge, of menstruation and of the nervous activities more or less specific for sex life are due to hyperfunction of the gonads. There is little or no support for such a conclusion from either the clinic or the laboratory. It is true that ovariectomy will stop menorrhagia, just as it will stop normal menstruation. Does that prove that menorrhagia is caused by ovarian hypersecretion? Not at all. The menstrual disturbance is just as readily explained by the action of qualitatively and quantitatively normal ovarian hormones on mechanism rendered hypersensitive by other factors. Given otherwise normal men and women, a hundred ovaries and a hundred testes instead of two would probably not increase the menstruation or the sex urge above the normal.

The question of toxic ovarian secretion has been raised in connection with osteomalacia. We have reports of cure of this malady by ovariectomy, also reports of failure of cure by ovariectomy. It is an open question. There is no evidence that the normal ovarian hormones have any special influence on the health of the bones.

The question of hyperfunction has also come up in connection with hyperplasia of the thymus, and with tumors of the pineal gland. Since extirpation of these glands produces no effect, it is difficult to conceive just how hyperactivity of the glands might cause disease,

Digitized by Google

especially if the thymus gland works by the method of detoxication. Pineal tumors might cause far reaching effects by mechanical pressure on the midbrain.

ALLEGED HYPO-ACTIVITY AND HYPERACTIVITY OF THE DUCTLESS GLANDS THROUGH DISTURBANCE OF THE NERVOUS SYSTEM

We have the following possibilities: 1. The endocrine glands may be under complete control of secretory nerves, like the salivary and the lacrimal glands, in which case we would expect hypofunction and atrophy to follow denervation. 2. They may have no secretory nerves, but may be controlled by the composition of the blood, as the kidneys are. In this case, the effect of denervation cannot be predicted. There may be hyperactivity, hypo-activity or no change in activity. 3. They may be controlled in part by secretory nerves, in part by the composition of the blood like the glands of the stomach. In this case also the effects of denervation might be zero. These appear to be the facts:

1. Sectioning of all the nerves to the ductless glands produces no demonstrable effect on the body functions, and no significant changes in the glands. The suprarenal medulla seems to constitute an exception to the second part of this statement. Denervation of the suprarenals induces no disturbance of body functions, except in the output of epinephrin. This is decreased or completely stopped. This shows that the output of epinephrin is under the control of vasomotor or true secretory nerves. It also shows that epinephrin is of little or no importance as a hormone.

2. Vasomotor nerves appear to be present in all the endocrine glands, and by histologic methods nerve filaments have been traced to or in close proximity to the gland cells themselves. In some of the glands, notably the pancreas, numerous ganglion cells are present in the peripheral nerve net. The suprarenal medulla, the posterior lobe of the pituitary and the pineal glands are modified nervous tissues, and these

Digitized by Google

glands may retain some of their original nervous connections.

3. What effects are produced by artificial stimulation of the nerves that go to the endocrine glands? Direct stimulation of the peripheral end of the splanchnic nerves augments the output of epinephrin, and ultimately exhausts the suprarenal medulla of epinephrin. The question of reflex and central control of this suprarenal nervous mechanism is unsettled. Competent investigators have reported absolutely contradictory results, and clinical opinions bearing on the question are mere guessing. This is the only securely established instance of nervous control of a possible endocrine gland, but the output controlled by the suprarenal nerves has yet to prove its right to be classed as a hormone.

The methods used in the attempts to demonstrate nervous control of the hypophysis have been shown to be unreliable. We have a mass of data, most of it contradictory, and the remainder not yet confirmed, on the nervous control of the thyroid activity. We may disregard the histologic reports and the alleged surgical cure of toxic goiter by section of the thyroid nerves (the cervical sympathetic). The change of iodin content of the gland on stimulation of the thyroid nerves is questioned, and even if such change should be conclusively established, the interpretation of the fact is uncertain. But there are two lines of experimental evidence that require serious attention. It seems to be a fact that stimulation of the thyroid nerves induces changes in the electrical potential in the gland (usually increased negativity but sometimes positivity). Similar experiments (pituitary injections) on the mammary glands have been reported as proving that pituitary extract causes secretion of milk. The electrical change following administration of pituitary extract is due to contraction of the smooth musculature of the mammary glands. Before the electrical variations

Digitized by Google

in the thyroid gland on stimulation of the thyroid nerves can be accepted as proving the nervous control of thyroid activity, it must be shown that the electrical change is not induced by the contraction (or relaxation) of the arteries, capillaries and veins in the gland. It is further reported that stimulation of thyroid nerves and mechanical massage of the thyroid gland in cats under light ether anesthesia accelerates the denervated heart. Massage of the thyroids for two minutes is reported to accelerate the heart for from thirty to ninety minutes after a latent period of from fifteen to twenty minutes. The investigators state that the experiment does not succeed in the months of March and April. The experiment, when successful, is interpreted as showing that mechanical massage and nerve stimulation increase the output of the thyroid hormone, which in turn accelerates the heart indirectly by increasing the body metabolism. It is pointed out as supporting evidence that mechanical massage of the suprarenals increases the output of epinephrin. We may note as equally true that mechanical massage of the kidneys, the pancreas, and the salivary and gastric glands, does not stimulate these glands to increased activity. The failure of the experiment in March and April is puzzling, as no one has shown any seasonal variations in the thyroid hormone of the cat. If the cat's thyroids are shy of iodin in March and April, such deficiency can easily be remedied by feeding iodids. But the most serious difficulty in accepting the positive findings as evidence of nervous control of thyroid activity is the prompt appearance and rapid cessation of the cardiac acceleration, the whole reaction being over within one to two hours, while it appears that a single intravenous injection of large or small doses of Kendall's thyroxin (a product assumed to be pure thyroid hormone) is reported to have no effect on the metabolism during the first twelve to twenty-four hours; then the increase in basal metabolic rate begins,

Digitized by Google

reaches its maximum increase in from three to seven days, and slowly subsides to normal in from three to six weeks. This, if true, is surely a different reaction from that described as following the massage of the thyroid or stimulation of the thyroid nerves.

The question of endocrine hypofunction and hyperfunction through direct nervous control is of great practical and theoretical importance. But despite the great amount of painstaking work in this field (and disregarding the still greater amount of speculation), it must be recognized that the entire question is an open one, except for the suprarenal medulla. Let us hope that the future will record better controlled observations and less speculation. But it seems to me that this statement is permissible: Endocrine secretory nerves, if present, play a minor or negligible rôle in the normal and pathologic activity of the glands, otherwise demonstrable disturbances should be produced by denervation of the glands. It should, of course, be recognized that extreme changes in nervous activity may induce endocrine hypofunction or hyperfunction indirectly or by way of the blood through changes in metabolism.

ENDOCRINE HYPOFUNCTION AND HYPERFUNCTION THROUGH MUTUAL STIMULATION OR INHIBITION OF DIFFERENT ENDOCRINE GLANDS

In this field appears the maximum of fiction and the minimum of established facts. The principal facts are these:

1. It appears that the ovaries and testes (at least in mammals) cannot develop or maintain their normal function in marked hypothyroidism or marked hypopituitarism.

2. Thyroidectomy and, in some species at least, gonadectomy induces some hyperplasia of the hypophysis.

Digitized by Google

3. Thyroid feeding in experimental animals over long periods appears to induce some hyperplasia of the suprarenals (and the hypophysis), but this has probably no direct endocrine significance, because the thyroid feeding causes at the same time hyperplasia of the heart, the liver, the spleen and the kidneys.

4. Hypertrophy of the parathyroids has been described in thyroidectomized tadpoles.

5. In some cases, tumors of the suprarenal cortex seem to hasten maturation of the gonads, and gonadectomy may be followed by hyperplasia of the suprarenal cortex.

6. Castration retards the involution of the thymus. This may mean that hormones from a mature gonad are directly or indirectly responsible for the post-adolescence involution of the thymus. It has no further endocrine significance, since evidence is lacking for any endocrine activity of the thymus itself.

7. It is reported that crushing the suprarenal cortex induces a temporary fever, and that the latter is aborted by thyroidectomy. Assuming this to be a fact, it might indicate a stimulating action of the suprarenal cortex on the thyroid, inasmuch as complete suprarenalectomy does not induce hyperpyrexia. But crushing the suprarenals is not a simple experiment, and we must await further work before the results can be clearly interpreted in the sense of mutual endocrine control. It may be noted in this connection that the feeding of suprarenal, that is, cortical residue or extract, is reported as a cure of toxic goiter. If toxic goiter means thyroid hyperactivity, this may indicate inhibitory action of the suprarenal cortex on the thyroid. But all of us know that the "cures" for mild cases of toxic goiter are legion, and severe cases may resist all available therapy, including rest and diet.

If the foregoing facts are restated in terms of endocrine interdependence, the situation is this: The fail-

Digitized by Google

ure of gonad function in hyperthyroidism is probably due to the profound distribution of metabolism. In cretinism and myxedema, there is evidence of degeneration or atrophic changes in most of the organs of the body. It is well known that depression of the gonads is a frequent effect of metabolic disturbances from faulty diets, as well as from chronic maladies resulting in cachexia. The failure of gonad function in frank hypopituitarism may also be due to the general impairment of growth and metabolism; but this is less certain, because the disturbance of metabolism in hypopituitarism appears to be less profound than in hypothyroidism. But we are not justified in interpreting the fact in the sense of a direct stimulation of the gonads by pituitary hormones, since pituitary feeding seems to have no influence on gonad development, and acromegaly itself may be accompanied by gonad depression rather than the reverse. The possible significance of the hyperplasia in some ductless glands following hypo-activity or hyperactivity in another gland system will be considered in a later section. At present, there is no evidence that hypo-activity or hyperactivity of any endocrine system, outside of the specific gland involved, can produce or prevent diabetes, myxedema, Addison's disease, infantilism or acromegaly. Despite this fact, the thyroid-pituitary-pancreas-suprarenal-gonad group will probably continue to be a favorite exercise ground for speculative physiology and therapy in regard to mutual hormone control.

THE QUESTION OF HYPERFUNCTION IN CASES OF GLANDULAR HYPERPLASIAS

There is a tendency among both laboratory workers and clinicians to interpret glandular hyperplasias, that is, increase in gland volume by increase in the number of apparently normal cells, as evidence of glandular hyperfunction. This interpretation is also applied to adenomatous hyperplasias, especially of the thyroid,

Digitized by Google

the pituitary gland and the suprarenal cortex. We must recognize that on the anatomic and histologic basis alone this interpretation is a theory that may be 100 per cent. correct or 100 per cent. wrong. We have some reliable histologic criteria of the state of secretory rest and secretory exhaustion in the case of the digestive glands, and previous degrees of activity of the digestive glands can be inferred by the degree of depletion of so-called secretion granules; but it must be recognized that this correlation of histologic changes with the state of activity would have been purely theoretical even for the digestive glands, except for the fact that we have a direct measure of the activity of the digestive glands in the output of the digestive juices. As previously stated, we have no certain means of directly measuring the rate of output or concentration of the hormones in the blood, except epinephrin, and this is not an important hormone, if it belongs in that group at all. Hence, we are limited to attempts to correlate gland histology with body symptoms that may or may not be specific effects of hyperactivity or hypo-activity of the gland in question. We have microchemical tests for iron, glycogen, fat, etc., in the cells, but none for the hormones.

It appears that thyroid colloids can be stained inside the thyroid cells, but we do not know the relation of thyroid colloid in the cells or in the lumen of the gland to the rate of output of thyroid hormone. Diagnosis of toxic goiter from the structure of the thyroid or the thyroid adenoma alone is, at present, merely guesswork.

In the same way, variations in kinds and numbers of cells or granules in the cells in tumors and hyperplasias of the hypophysis, particularly if the studies are made on ordinary postmortem material, permit no conclusion as to hyperfunction. And the situation is scarcely better in regard to the relation of the pan-

Digitized by Google

creas to clinical diabetes. Postmortem examination reveals a high percentage of pancreatic lesions in persons having no diabetes. The hydropic degeneration of island cells usually found in the pancreas of diabetic patients is regarded by some as one of the *effects* of the diabetes. It is generally agreed that many cases of fatal diabetes could not have been diagnosed by the histology of the pancreas alone. It is probable that increase or decrease in some cell functions antedates structural changes in the cells as revealed by present methods.

In recent years, much attention has been given to the endocrine glands as related to various types of nervous disorders. The difficulties in this field are increased by the fact that we have as yet no reliable method of studying functional nervous disorders in animals under experimental interference with the ductless glands. By the law of chance, some endocrine disturbance will be present in a certain percentage of insane persons, even if there is no causal relationship between the two phenomena. The literature records a high percentage of what appears, microscopically, to be pathologic endocrine changes in necropsies of such patients. The significance of such pathologic endocrine changes (mostly hypoplasia or atrophy), in the cause and course of the nervous disease, is most uncertain, especially when physical or physiologic signs of specific endocrine dysfunction are lacking. Such endocrine changes may have no more significance than the high percentage of destruction in the pancreas in persons past middle life, dying from diseases other than diabetes.

We have examples of endocrine therapy in nervous disorders that display the courage of ignorance. I do not know what you think of suprarenalectomy as a cure for idiopathic epilepsy, but for the present I would leave the suprarenals alone and operate on the patient's pocketbook by some other route.

Digitized by Google

Has, then, the microscope ceased to be a useful tool in biologic investigation? On the contrary, let the tribe of microbiologists increase. But I plead for greater discernment in the physiologic interpretations of microscopic findings.

THE EVIDENCE FOR ENDOCRINE HYPOFUNCTION AND HYPERFUNCTION FROM THE FIELD OF ORGANOTHERAPY

Except for the condition of hypothyroidism, the extensive literature on clinical and experimental organotherapy has so far yielded little or nothing conclusive touching endocrine dysfunctions. This should cause no surprise. Organotherapy can have no effect in maladies due to dysfunction of ductless glands that function on the principle of detoxication. And in the case of glands that function by producing hormones, organotherapy may fail now and forever, (1) if the hormones are not stored up in the gland; (2) if they are too unstable for the necessary chemical processes of isolation for intravenous or hypodermic administration, or (3) if, on oral administration, they are destroyed in the processes of digestion and absorption.

With the exception of the thyroid hormone, and the drugs epinephrin and pituitary extracts, we literally do not know what we are feeding when hypophysis, suprarenal, testes, ovaries, pancreas or parathyroid preparations are administered to patients. Moreover, the specific endocrine factor in the malady in which organotherapy is tried is often a matter of conjecture. That is to say, we are administering "unknowns" to cure diseases of unknown origin.

Organotherapy has been tried in literally every disease known to man. Except for the thyroid, the results are so conflicting that they seem to depend, not on drugs, but on the physician who prescribes them. Fifteen years ago, Pohl's spermin or testicle extract was a cure-all in Russia; today, pluriglandular pro-

Digitized by Google

prietaries are doing even greater wonders in our country, according to the testimonials. Let us keep a few things clearly in mind in this connection:

1. So far, it has not been possible by organotherapy to appreciably influence the impaired functions due to gonadectomy, ovariectomy, parathyroidectomy, pancreatectomy[1] or hypophysectomy in animals. In these cases, we know at least the initial pathology, even if we do not know what we are feeding in the gland extracts.

2. The history of medicine and of quackery teaches honest men to be slow in ascribing specific values to any therapeutic measure that seems to improve subjective symptoms, or to cure in the field of the functional nervous diseases.

3. The trial-and-error method, or empiric organotherapy, is a legitimate path to follow. But I think you will agree with me that it is not a path of progress when the trials are so made that nothing but error can result from them. The trial frequently consists in: improved diet, rest, and gland extracts; the error is the conclusion that the gland extract is responsible for the improvement of the patient. Let us not forget that thyroid administration, even in frank hypothyroidism, is in many cases not a complete substitute for the normal thyroid. And thyroid therapy is our best, if not our only case.

It is scarcely necessary to refer to the ease and assurance with which alleged endocrine disorders are diagnosed and treated with gland extracts by men of good standing in the medical profession. Some aspects of the literature on glandular extract therapy today remind one of the age of demonology in medicine. Following are four typical citations, not from Alexander Dowie, Louis Berman or Mary Baker Eddy, but from our respectable medical journals:

1. Work in progress at the University of Toronto seems to promise more positive results from the pancreas hormone in experimental diabetes.

Digitized by Google

Clinical studies have proved that certain physiologic and structural markings are constant to certain glandular types, and by physical objective examination alone without other information we can make an accurate diagnosis.

The alert, aggressive attitude of the healthy young man, and the similar, though feminized, pose of the healthy young woman, are in large part an evidence of thyroid activity. The tremors, and blushes, the sentiment of the young woman, the nervous apprehension of the young man under emotional stimulation are also largely evidences of thyroid activity. The blushing of the sensitive young girl or boy is but a neurocirculatory reflex exaggerated by thyroid overactivity into the neurocirculatory instability of the definitely hyperthyroid patient.

Periods of great emotional output, such as courtship, early months of marriage, and the more active phases of an artist's career, are accompanied by enlargement of the thyroid.

There is also something closely allied to a diminished action of the thyroid gland that renders the old maid less generous and less spiritually beautiful than the pregnant woman.

EVIDENCE OF ENDOCRINE HYPOFUNCTION AND HYPERFUNCTION FROM THE FIELD OF ROENTGEN-RAY THERAPY

The destructive action of the radium and the roentgen rays on tissues is well established; and it is well known that atrophy and hypofunction of such organs as the thyroid, the ovaries and the testes can be induced by these agencies. On the theory that doses of roentgen rays, too slight to destroy, will stimulate and thus increase the normal functions of glands, the pancreas has been roentgen rayed in diabetes; the hypophysis, in Fröhlich's syndrome, etc. Positive results have been reported, despite the fact that careful experiments on glands, where the activity can be measured with quantitative and qualitative accuracy, have shown only destructive actions by the roentgen ray. An almost miraculous result is reported in the case of a 15 year old boy with some Fröhlich's syndrome signs. "After four roentgen-ray irradiations of the hypophysial region, the penis grew 8.5 cm. in three months." Evidently, we are witnessing the beginning of a race

Digitized by Google

between roentgenologists and surgeons as harbingers of virilism.

The possible stimulating action of radiant energy on the ductless glands should be tried, but tried under conditions that permit the evaluation of the results. At present, we do not possess any certain means of stimulating any ductless gland, "gently" or otherwise, except possibly through the food, and this is probably not specific. Those who speak with such ease and assurance of "stimulating" this, that or the other endocrine gland are merely giving a demonstration of their ignorance.

THE ETIOLOGY OF ENDOCRINE APLASIA AND HYPERPLASIA IN MAN

Destructive lesions of the endocrine glands, such as tumors, tuberculosis, cystic degeneration and fibrosis, are not peculiar to these organs, and consideration of the etiology of these lesions would take us too far afield.

Factors that may be primary in other aplasias and hyperplasias are: heredity, undernutrition, intoxication from deranged metabolism (qualitative and quantitative) and infections (specific and general).

The possible hereditary factors have not yet been seriously investigated.

Some of the ductless glands appear to be readily disturbed by undernutrition, or unbalanced diets. It is fairly certain that some iodin in the food is necessary for the normal activity of the thyroids. There is considerable literature pointing toward infection as the primary factor in certain types of thyroid hyperplasia. But the question is still open. It is possible that endocrine aplasias and hyperplasias are induced by a variety of factors. Research in this important and difficult field is being neglected in comparison with the amount of attention devoted to the

Digitized by Google

less difficult and more spectacular (and remunerative) administration of gland products.

CONCLUSION

No single phase of endocrine dysfunction is satisfactorily worked out today, either clinically or experimentally. I have endeavored to present the established facts and what appear to be obstacles to progress in baseless speculations and uncritical practice. I am not foolish enough to believe that the former is free from flaws, and some of you may feel that my strictures on the latter are too severe, especially coming from an experimental physiologist. But I have not spoken as a pharisee or as a mere arm-chair iconoclast. The credit for progress made and the blame for errors committed are shared by the clinical and laboratory groups. I leave out of consideration the hopelessly ignorant and the actually dishonest who, no matter what their position and training, belong to the genus *quack*. One sure way of inviting defeat is to underestimate the resourcefulness of the enemy. Failure to recognize the complexity of every endocrine problem is an equally serious obstacle to victory. In following the hormone theory alone, we may, in the case of some of the ductless glands, even be way off the main road.

I believe that much of the glandular therapy of today, however harmless to the patient, injures the good name of the medical profession with intelligent laymen. We cannot practice quack methods and escape the just censure of society.

The quack diagnoses every ailment with ease, and offers remedies for every disease with assurance. The good physician knows that he is neither omniscient nor omnipotent in the field of disease; and the educated layman knows this as well as the physician. Then, why pretend? Bluff may succeed for a time, but honesty is better for society; and what is best for society is

Digitized by Google

best for the medical profession. It is related, in the most ancient medical record now known, the Smith Papyrus, that the good physician in Egypt 5,000 years ago practiced medicine with the same honesty and the same quality of intelligence as that of the good physician of today. When physicians of that age knew, or thought they knew, that no available remedy would help the patient, they did nothing, while the quack worked his "cures" with the hookums of that age.

Digitized by Google

SOME PRINCIPLES OF ENDOCRINOLOGY APPLICABLE TO ORGANOTHERAPY

R. G. HOSKINS, PHD., M.D.
Professor of Physiology, Ohio State University College of Medicine
COLUMBUS, OHIO

In a field of biology the bibliography of which runs to 500 pages, the need for the formulation of principles might be expected long since to have passed.[1] To any one conversant, however, with the endocrine literature, it is obvious that no general agreement on principles—and hence on practice—has yet been reached.

Endocrinology is to an unusual degree an empiric field. Our fundamental conceptions have been attained largely by clinical observations of end-results rather than by rational induction from basic facts determined, after the approved fashion, by controlled experimentation. Empiricism has deserved much of the odium that it carries. That it has a legitimate place in medicine, however, is tacitly conceded by every one who prescribes any medicament the pharmacology of which is not fully known. Indeed, it has often been said that the value of any procedure in medicine must finally be determined empirically in the crucible of the clinic. The figure is apt; but let us recognize that a crucible is not an open hearth into which junk may promiscuously be thrown, nor is the result of a crucible test determined by the amount of smoke and spluttering produced. The only empiricism that is of value is that which results in well substantiated facts. When these facts can be adequately systematized they become science; but as facts, they are no more true than they were before.

1. The bibliography of the fourth edition of Biedl's Innere Sekretion comprises 474 pages, and many articles have appeared since the published list was completed.

Digitized by Google

Much of the existing confusion in the endocrine field would appear to be due to overanxiety to escape the reproach of empiricism—to force rationalization when no genuine rationalization is possible. In such attempts, one class of writers habitually misuses the form of inductive logic, selecting from the vast accumulation of data such as appeal to them, and ignoring such as are inconvenient. Thus, their basic "principles" are derived. Any writer adopting this method has no grounds for complaint that his dishonesty in dealing with the data of others leads to the conviction that he is equally dishonest in dealing with his own. The device of attempting to escape the necessity of patience and thoroughness by dubious theorizing should be discarded. It has brought contempt upon much that passes as endocrine literature.

ENDOCRINE ORGANS AND THEIR FUNCTIONS

So far are we from accepted principles that it is not amiss, even at this late day, to inquire, What is an endocrine organ? Gley has formulated three determining conditions. The gland must show the histologic picture and the cytologic polarity of a secreting structure. This principle at once excludes from the endocrine congeries the thymus gland and the neural lobe of the hypophysis; but these in many circles are still in good and regular standing. A second principle is that from the organ in question an active substance must be obtained. Such a substance may be, but probably is not, a hormone. Final logical proof demands that the peculiar principle be detected in the effluent blood or lymph. In case of nearly all the assumed endocrine structures, this last step remains yet to be taken.

It is widely assumed that perturbed function in any one gland is characteristically followed by changes in others. It is presumed that any endocrine gland may show a condition of normality, hyperfunction, hypo-

Digitized by Google

function, dysfunction, dysfunction plus hypofunction, or dysfunction plus hyperfunction; that is, one normal and five abnormal states. Theoretically there exist, therefore, five uniglandular syndromes for each endocrine organ. The more enthusiastic endocrinologists assert the existence of at least nine endocrine organs, each of which presumably can assume any one of the six states. The possible number of basic combinations, then, is six to the ninth power, or 10,077,696. One of these combinations is normality of all glands; hence the theoretical number of endocrinopathies is 10,077,695. If one is more modest and assumes the existence of only six glands, there are but a paltry 46,655 possible endocrinopathies.[2] To what extent these may be modified by relationships of vicarious function, interstimulation and interinhibition of varying degrees, one cannot offer even an intelligent guess. In any case, however, few of the theoretically possible endocrinopathies have ever been recognized clinically, and of these, still fewer have been reproduced experimentally. When each factor in each syndrome can be recognized and appraised, clinical endocrinology will have become a science. By that time even medicine as a whole may conceivably have become a science.

SOURCE AND VALUE OF GLANDULAR PRODUCTS

Perhaps the most interesting immediate question to the practical endocrine therapist is, From what glands can active hormone products be derived? Judged by the "therapeutic test" in the hands of credulous impressionists, the number is extensive. The number for which there is adequate proof is much smaller. The proverbial "crucible" is still spluttering. The most convincing evidence on this point is being obtained by investigators on tadpoles. Seemingly, a healthy tadpole is vastly different from a sick woman. Practically, the tadpole is a very delicate physicochemical indicator of

2. I am indebted to my colleague Prof. W. M. Barrows for this mathematical formulation of the situation.

Digitized by Google

the operation of factors that modify vital processes; and the determination of such factors is the primary problem of the endocrinologist.

As to the clinical value of glandular products now available, much uncertainty exists. There is great need of standardization of methods of manufacture and of assaying. Even granted an endocrine function for a given gland, the quantity of hormone present at any one time may be very minute. Moreover, even if it exists in relatively large quantities in the fresh gland, there is no certainty that it will not all be lost in the manufacture of gland products. Furthermore, we know little as to the extent to which hormones are absorbed or destroyed in the alimentary tract. It would seem wise for the present for the individual observer in practical work to adopt some one preparation of each gland and use that exclusively for considerable periods. This would help to eliminate one of the variables that render the therapeutic literature so difficult to evaluate. It would also be desirable, until the actual value of each product is determined, to use fresh gland substance; but this is usually impracticable. It would be practicable, however, to obtain, in many cases, desiccated material that has not been subjected to any process of extraction or chemical treatment. From the standpoint of the pharmaceutical manufacturer, such a suggestion is not attractive; but a large body of evidence regarding the efficacy of the unaltered gland substance is needed as a basis from which to determine the relative value of special products. The ideal state will, of course, be reached when each active principle has been isolated and synthesized. If organotherapy ever takes the place that its more enthusiastic proponents prophesy, the available supply of natural products will be vastly inadequate. It is said, for instance, to require 5,000 calves to produce a pound of desiccated pineal substance.

Digitized by Google

REACTIONS

Another question of major importance has scarcely as yet been even considered, namely, What conditions modify the reactions to any given hormone? In case of epinephrin, it has been shown that the vasomotor reactions are diametrically opposite, depending on initial blood pressure, bodily vitality and temperature, dosage, reaction of the menstruum, and depth of anesthesia. In case of the thyroid there is evidence that change of dosage may reverse the reaction from anabolic to catabolic. Pituitary extract causes or checks diuresis, depending on attendant conditions. It is not unlikely that similar reversals of reaction will be found in the case of other gland products.

In the case of products that influence growth, the normal occurrence of proliferative cycles is of considerable importance. A given hormone might materially influence developmental processes at one time and be quite without influence at another.

A principle worthy of particular stress is that a given endocrinopathy may be readily amenable to treatment in its earlier stages, but quite intractable, later. Skeletal growth, for example, can no longer be influenced after closure of the epiphyseal junctures. Early diagnosis and early treatment are therefore of the utmost importance.

OBJECT OF ORGANOTHERAPY

Endocrine products may be prescribed with several purposes in view. The most definite is merely to compensate additively for a deficient hormone. Thyroid gland is thus administered for myxedema. The possibilities of even this type of therapy, however, remain yet largely to be determined. Hallion has suggested that gland products often act by stimulating the homologous gland. This statement has been accepted by some writers as a biologic law. There is some definite evidence in its support, but the extent of its

Digitized by Google

applicability remains for future determination. As to the usefulness of gland products to inhibit antagonistic glands, we have little significant information. Desiccated pancreas is said to depress the activity of the suprarenal glands, but what is apparently meant is that it is a slowly acting vasodepressant. If it be such, the substance may be of practical value; but there is little rational basis for regarding it as a suprarenal antagonist.

The use of endocrine products for their purely nonspecific pharmacologic properties offers a promising field for further investigation. The use of epinephrin and pituitary extract has been especially stressed. As regards pituitary extract, the prevailing opinion of recent years has tended toward conservatism. There are even extremists who would banish it from the field of obstetrics on the ground that the reactivity of patients varies so widely as to render it always potentially dangerous. The sublingual administration of the drug, however, would seem largely to eliminate danger and to widen materially the indications for its use in any condition wherein a general smooth muscle stimulant is indicated. Another promising field for therapeutic investigation is the utility of thyroid as a nonspecific drug. The thyroid hormone appears to be a general cell stimulant, and hence to be widely indicated in conditions in which depressed functional activity is a predominant feature.

DOSAGE

One of the most troublesome problems in organotherapy is that of dosage. In addition to variability of products, the variability of patients is striking. In current practice a given substance may be administered in quantities varying from a fraction of a grain to a hundred grains. In case of the thyroid, basal metabolism affords a control. It has been suggested that the dosage of desiccated hypophysis can be determined by

Digitized by Google

the administration of increasing amounts to the point of producing headache, and then dropping to about half of this dosage. Empirically, it seems to be fairly clear that alternate periods of administration and of rest give best results.

At present there is much difference of opinion as to whether endocrine products should be prescribed singly or in combination. Looking to the interest of humanity at large, present and future, single products should be employed whenever there is a reasonable chance of their proving helpful. In this way only can we hope within any reasonable time to determine the independent value of each product. Whatever be the intricacy of organ involvement in the various endocrinopathies, it is to be supposed that ordinarily some one gland is primarily at fault. Biedl has stressed the fact that, with correct diagnosis on this point, uniglandular therapy may give brilliant results.

On *a priori* grounds, however, if endocrine syndromes are, as many maintain, always, or even commonly, pluriglandular, more rapid amelioration might be expected if a suitable pluriglandular formula were used. Practically, rational pluriglandular therapy would seem to demand a large number of different combinations, and these in differing proportions in each case, as indicated by the degree of involvement of each gland and the susceptibility of the patient.

It has been suggested that the free use of pluriglandular formulas is desirable on the supposition that the body cells will select those hormones needed and discard the rest. This theory apparently embodies a half truth. That the various body cells do select from the blood stream the substances necessary for their metabolism is obvious: the sphenoid bone and the vermiform appendix are fashioned from the same pabulum. That the body cells are able to reject any hormone, however, I know of no evidence; whereas, it is known that hormones are often assimulated by body cells to their

Digitized by Google

own detriment or even death. In any unanalyzed syndrome, it would seem that a random hormone would be potentially harmful to the same extent that it would be potentially helpful.

CONCLUSION

It seems desirable again to emphasize the complicated nature of the problems with which the endocrine therapeutist is confronted. Little is to be expected from nonchalant attempts to solve these problems by superficial observations. Nor can a thoughtful clinician take seriously the claim that overenthusiastic use of gland products is to the best interest of the patient. The arguments adduced are precisely the stock arguments of the cultists and nostrum venders. Ultimately, practical organotherapy will have to be reduced to a statistical basis. This will require the accumulation of a much greater fund of well established observations, both positive and negative. There is need for many more careful studies of individual cases as well as extensive series of cases. Almost any endocrine case presents a research problem worthy of exacting study.

Individual endeavor by volunteer investigators is making some headway, but progress is necessarily slow. There is need for the founding of one or more well equipped and well financed institutions devoted specifically and in a large way to endocrine research. Such an institution should include a hospital with personnel and equipment for bringing to bear the best modern diagnostic and therapeutic technic, and especially for careful metabolic studies. In association with this hospital there should be provided adequate facilities for coordinated animal experimentation.

Endocrinology in some form is going to flourish indefinitely. Parlor endocrinology is even displacing parlor Freudism. For better or for worse, endocrinology has acquired a recognized place in the field of medicine. For two decades practitioners have been avidly seeking enlightenment regarding the practical,

Digitized by Google

everyday problems with which they are confronted. As to how their needs have been met, let the present state of organotherapy testify. The problems offered are such as to tax the best efforts of the best trained therapeutists. Shall these gather their robes about them and pass by on the other side? To the extent that enlightened, critical leadership fails, to that extent will cheap, commercialized endocrinology have a large following, and medicine be cheapened to the same degree.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. BARKER, CANNON, AUB, CARLSON AND HOSKINS

DR. WILLIAM ENGELBACH, St. Louis: As a whole, the symposium impresses one with the hypercriticism of those men who are seriously taking up the study of internal secretions. It gives a good general perspective of the relative importance of the internal secretions. The disorders of the ductless glands are only a small part of internal medicine, but this small, yet important, field has been greatly neglected. The most dangerous thing that confronts clinicians is the early misinterpretation of pathologic endocrine signs present in many normal persons. We each belong to a certain endocrine type, and we have to go farther than the establishing of a type picture to make a diagnosis of a ductless gland disorder. For instance, if a person has headache and he happens to be of the acromegalic type, it does not follow that the headache is of hypophysial origin. There has to be more evidence of pituitary disorder before that relation can be proved. The relation of the sympathetic nervous system to the ductless glands and the body as a whole must be given more consideration. As pointed out by Dr. Cannon, the clinical experiments on vagotonia have been of value in excluding the positive basis on which this complex was introduced. I regret that Dr. Aub did not say more about those peculiar adiposities related to pituitary disease with a low basal metabolic rate. The most recent literature credits the pituitary gland with diminishing metabolism. As that metabolic rate is taken today, based on the oxygen exchange in the lungs, comparatively all these patients having pituitary adiposity experience no change in their basal metabolic rate, yet they gain weight rapidly. It will be necessary to have other tests—fat metabolism must be investigated, with other estimations of metabolism before this is explained. The cooperation of the best men in their various experimental departments will promote a better understanding of this complex subject. Dr. Hoskins' paper is timely in that it draws attention to the varied terminology and nomenclature

Digitized by Google

prevalent at this time. Terms such as dystrophy and dyspituitarism, used as a cloak for ignorance, should be abandoned. The physiologists have not proved that we have a specific substance from some of these glands. There is no question that there is overenthusiasm in the treatment of ductless gland disorders. Undoubtedly, we can accomplish more by uniglandular treatment, even if we have a pluriglandular disorder. Make the test with one gland substance for a long time to determine whether you get a therapeutic reaction, and then, if you think there is another gland involved, give the other substance singly, noting results. Stock prescriptions of pluriglandular substances are difficult to control or estimate. For instance, a preparation containing one-half grain of thyroid, combined with epinephrin and spermin, given to a person who needs 5 grains of thyroid substance would be insufficient to meet indications. We have to know how to give each glandular substance up to the physiologic effect, and this varies in each individual patient.

Dr. Leonard G. Rowntree, Rochester, Minn.: Endocrinology is still young. It is far from a science. Facts are being pried from nature, and these facts are being scrutinized, systematized and correlated. Science will eventually evolve. The need in endocrinology today is, as it always has been, well planned and carefully executed clinical and experimental investigations, accompanied by analytic and critical judgment. Dr. Cannon has dealt largely with matters pertaining to the control of the activity of the endocrine glands, considerations which led Bayliss and Starling years ago to the discovery of hormones. To this field, Dr. Cannon himself has contributed much. He demands facts and not speculation, and it was extremely interesting to hear him say that he hints at correlation of function, but needs more evidence before accepting these correlations. Dr. Aub reports the results of studies where, happily, objective control is possible. He has furnished a model in the differentiation of facts from hypotheses and theories and he has made contributions to our knowledge of the factors involved in the control of metabolism and the mechanism involved in this control. Dr. Carlson has directed a searching inquiry into many of our physiologic and clinical beliefs, and has emphasized particularly the shortcomings of clinicians and also of physiologists. As a physiologist, he has subjected to critical judgment our claims concerning the qualitative and quantitative changes resulting from manipulative procedures or from processes of disease. He has attempted correlations of clinical, physiologic and pathologic data which, in part, have puzzled and baffled clinicians and which apparently are also somewhat puzzling and baffling to him. Dr. Hoskins has emphasized the magnitude of the therapeutic problem and has called on the leaders of the profession to exercise leadership in therapy as well as in diagnosis. There are certain needs in endocrinology: (1) postulates in endocrinology analogous to Koch's postulates

Digitized by Google

in bacteriology; (2) a common basis among workers in the same field, and between workers in the various fields concerned in endocrinology, from the standpoint, first, of a common point of view, and, second, of nomenclature (Does hyperplasia, for instance, mean the same thing to all workers in all fields? Does it mean the same to all pathologists?); (3) clinical classifications and (4) objective control of therapy, such as we have in basal metabolism, urine output under the action of posterior lobe of the pituitary and blood pressure in Addison's disease. Progress in endocrinology will come slowly through thoroughly correlated, adequately controlled investigations, in which the findings are subjected to interpretation based on analytic and critical judgment.

Dr. Walter M. Boothby, Rochester, Minn.: In a myxedematous patient, 10 mg. of thyroxin, injected intravenously, elevates the basal metabolic rate on the average 28 points. The height of the curve comes from the fifth to the tenth day after injection; it remains at this level for several days, and then gradually declines, reaching the original level from fifty to sixty days later. In the clinical administration of thyroxin or thyroid extract this delayed and long continued action of thyroxin must be taken into account in the determination of the size of the dose; also the fact that any change in the dose will not produce its main effect for five or ten days. Failure to appreciate this delayed effect has made it difficult to regulate properly the amount of thyroid extract required, and has led to the custom of intermittent administration. It is better, however, to establish a correct dose that can be given indefinitely; and it has been found that 1.6 mg. of thyroxin is usually the correct daily dose. The curve of the calorigenic effect of epinephrin is similar in form to that of thyroxin, provided that the time element is changed to minutes in the former case from that of days for thyroxin. In confirmation of Dr. Aub's work, we have been able to show in dogs that it is possible to obtain a calorigenic effect from such doses of epinephrin as Cannon and Stewart and Rogoff have shown to be within the powers of the suprarenal glands to secrete.

Dr. H. T. Hyman, New York: I was glad that Dr. Cannon called attention to the work that renders untenable the tonicity theory of the regulation of the involuntary nervous system. Dr. Cannon presented again his emergency theory and the evidence favoring it, but did not refer to the work at Western Reserve University which refutes many of the experiments on which the theory rests. With reference to the nervous influences on the thyroid, two facts are contrary to the evidence on which the supposition rests: 1. Thyroxin effects do not occur for hours, even days, after injection, while the supposed increased output of thyroxin following nerve stimulation is manifested in a few moments in the experiments quoted. 2. The supposed effect of the increased thyroxin output in the experiments of Levy we have produced

Digitized by Google

weeks after thyroidectomy and have shown to be due to changes in the involuntary nervous system. We are indebted to Drs. Carlson and Hoskins for their interpretation of clinical results. We know that it is necessary to ablate about 90 per cent. of a gland in order to produce evidences of insufficiency in the laboratory; that even with a fragment of active glandular tissue remaining, normal function is maintained. Under these circumstances, where is the evidence for the much discussed formes frustes? So far as we know, no gland can function for another. Where, then, are the evidences for vicarious functioning? How can endocrinologists refer to results following endocrine therapy as "specific results" when we have no means of assaying glandular preparations and when we know nothing of the absorption? We speak of hyperfunction. When we are unaware of the output into the veins of the glands under normal conditions, how can we postulate a hyperfunction? Most of the symptoms attributed to disturbance of the ductless glands can be produced only through the involuntary nervous system. Consequently, no more important step in our knowledge must be sought than the mechanism by which the ductless glands affect the involuntary nervous system.

DR. WALTER TIMME, New York: Dr. Hoskins' mathematics are very simple algebra—on the basis of permutations and computations. As a matter of fact, that principle of mathematics depends on constant quantities. The endocrine system has no constant quantities, only variables, and that needs a higher type of mathematics—a calculus which furnishes information about differentials — but the end-result has to be integrated by integral calculus. So we are still further along than we were before and at the same time more deeply involved. The answer to any integral calculus problem dealing with variables is never one term or absolute quantity. It is always represented in a series of terms combined in a formula of functions of the factors involved. To illustrate: A middle aged woman gives the clinical aspects of myxedema. Her basal metabolic rate was determined by three investigations made by two investigators, and varied from plus 80 per per cent. to plus 100 per cent. Hence, the men who saw her refused to believe it was myxedema and refused to give her thyroid. Examining the case further, we found that she had intense headache, and roentgenographic examination showed she had an enlarged sella turcica and a bitemporal hemianopsia with a diminution of vision. Therefore, it was a case of hypophysial mass, plus myxedema. She was given small doses of thyroid. Within two or three days she began to improve; her headaches began to diminish in severity, and the basal metabolic rate became lower, on no other treatment than the administration of thyroid! It does not mean that the deficiency of the thyroid produced a high metabolic rate; that the hypophysial mass produced the high metabolic rate; the high rate may be due to pressure of the

Digitized by Google

hypophysial mass on parts of the brain. In any event, it means that the integration of the syndrome is a formula, and that is what we have to consider in all the innumerable problems which confront us, and the formula is one which involves all the varying activities of the glandular elements.

DR. A. S. BLUMGARTEN, New York: I can discuss the subject only from its clinical aspect, and there are two phases to that: one is the importance of endocrine study in clinical medicine, and the other is the question of therapy. The study of the patient from an endocrine point of view is a valuable adjunct to the ordinary routine physical examination, especially when it is impossible to recognize a pathologic change by present methods of examination. Clinically, endocrine disturbances that are presented for treatment are usually disturbances in growth and development, and in physiology. In the majority of instances, the disturbances in development are not amenable to treatment by organotherapy, although the endocrine basis for the condition is apparent. The dried extracts of various ductless glands have a limited value, but it is hoped that we shall be able to get better results when we can better recognize the conditions amenable to treatment and have products which can give definite reliable effects. The basis of organotherapy is substitution therapy. One must be guarded, however, in drawing conclusions, as frequently spontaneous cures and improvements take place. For example: In the Froelich syndrome of pituitary disturbance, the improvement in genital development following pituitary therapy is often not the result of therapy at all. Many of the genital symptoms are merely a retarded puberty, which gets well spontaneously, even without therapy. The dosage is another important point in organotherapy. Since we are supplying a deficient substance and we have no way of determining the quantitative deficiency, we have no way of determining the dosage. I think we can summarize the present status of organotherapy in reference to dried extracts by stating that thyroid extract is curative in cases of thyroid deficiency, such as myxedema and cretinism. Pituitary extracts are valuable in relieving many of the symptoms of pituitary deficiency, largely of a subjective nature; and more valuable in females than in males. Objective results with pituitary extracts are rather rare. The other dried extracts are still in the experimental stage. Epinephrin and pituitary extract are useful for the production of their specific pharmacologic effects. The problem of the future consists in recognizing specific states of glandular deficiency and obtaining preparations that will produce definite results.

DR. HARRY A. BAKER, Minneapolis: There is a gland of which no mention has ever been made, important in the arrangement and, etiologically, a factor in the derangement of this system, i. e., the brain. Indeed, the brain ought to be included among the endocrines, for though, perhaps, through its subsidiary glands it is occupied in other activi-

Digitized by Google

ties, its chief function is the assimilation of matters sensate into sense and understanding. By regarding the brain as the head and front, and the sympathetic nervous system as the equilibrator, it then becomes easy to comprehend how disturbances primarily of the head result in functional derangements, faulty equilibration in metabolic disorders, and the reverse, faulty equilibration continued over a long period of time, resulting in minor or even grave functional disturbances, the relationship being almost as close as the cardiorenal to the organic system.

Dr. Louis B. Wilson, Rochester, Minn.: In this congeries of clinicians, physiologists, biochemists and mathematicians I, an old time pathologist and morphologist, feel like one of the slow going high wheeled ox carts of my adopted state in a flock of aeroplanes. But I wish to say one word of suggestion to the aeronauts: Keep close to the ground when you start, remembering that almost all that we know of the actual facts of disease has been learned at the necropsy table. Let us not forget that there is, after all, something in morphology which we cannot ignore in our experimental or physiologic or biochemical work on disease. One of the essayists doubted somewhat the correlation of the morphologic evidence of increased activity in the thyroid in relation to hyperthyroidism, because there is an occasional instance in which hypertrophy and hyperplasia of the cells of the thyroid are not coincident with what the clinician says as they appear in the patient. Clinical evidence, you know, is not always absolutely true. Neither is experimental evidence always true. I do not find absolute agreement in the pathology and in the diagnoses that have been made. There is just a suspicion that the patient did not have what the eminent clinician thought she had. When one essayist says he doubts the relationship between parenchymal overgrowth and overfunction in the gland, I think back over the seventeen years that I have spent in examining more than 16,000 thyroids—minutely, not in a single section, but going over them piecemeal by the hundreds of sections—and when I look at my photographs, I ask myself, "Have I been mistaken? Is it after all true that there is not any difference between the histologic evidence, and the facts as shown by the clinician, or as thought to be present by the clinician?" We must keep our feet on the ground.

Dr. W. B. Cannon, Boston: Dr. Carlson minimized morphologic change as indicative of disturbed function, and yet he used as part of his evidence that nerves are of minor importance for endocrine glands the fact that after nerve section there is little glandular change. There is good reason why we might not expect much change under these circumstances, for the glands supplied by nerves may also be subject to humoral control. I would agree with him that morphologic evidence does not answer the question of nervous

Digitized by Google

control. Both Dr. Carlson and Dr. Hyman threw doubt on our evidence that the thyroid gland is subject to nervous control. The reason for their doubt was that the substance thyroxin is not effective for twelve or sixteen hours, whereas on stimulation of the cervical sympathetic nerve the effect on the heart begins within 15 minutes. There is a discrepancy, but why is the doubt thrown altogether in one direction? Thyroxin is removed from the thyroid gland, but it has been put through complicated chemical processes, which probably have not left the active agent in its original state. To assume that because it accelerates metabolism it is the natural physiological agent in thyroid activity is not good reasoning. Possibly thyroxin requires time to become restored to its effective state. In our experiments massage or nerve stimulation or asphyxia was induced, and the observed effects could properly be regarded as physiological. Dr. Hyman asked why I did not call attention to observations made by workers at the Western Reserve University. I have so recently criticized this work that it did not seem necessary to repeat that their explanations do not explain their results, that the amount of epinephrin set free under stimulation is more than ten times that assumed by them to be constant, and that although they used quantitative methods, they lost an unknown amount of the secreted epinephrin in preparing it for quantitation. Dr. Levy's experiments have been criticized. It is a question of controls. He has recently informed me that he had five controls, animals in which the thyroid gland had been removed previous to the experiment; neither stimulation of the cervical sympathetic or large doses of adrenalin had any effect under these circumstances, though they were markedly effective when the thyroid gland was in the body.

Dr. J. C. Aub, Boston: As to the metabolism in Addison's disease, I was careful to avoid going into the subject. In the first place, I do not think Addison's disease shows an abnormal metabolism; in the second place, the thyroid may well maintain a normal metabolism although the suprarenal may be disturbed. I have been able to find four cases recorded in the literature. These cases, however, have shown a lowered metabolism. I do not think that proves the situation, and I do not think an abnormal metabolism would be found in the disease.

Dr. A. J. Carlson, Chicago: If time had permitted me to read the complete paper, I think Dr. Wilson would have agreed that my feet were on the ground and that I in no wise deny the histologic findings of Wilson and others on toxic goiter thyroids. I merely question the usual interpretation of the facts. A slide of a toxic goiter thyroid is today no scientific evidence of hypersecretion. I am pleading for care in the interpretation of the histologic findings. The actual facts we all accept, but some of us cannot accept interpretations as facts. We have no intracellular microchemical

Digitized by Google

tests for any secretion of the ductless glands, except, possibly, the suprarenal medulla. We can stain the thyroid colloid in the cells, but we do not know the relation of the thyroid colloid to the secretion. I have my feet on the ground, I think, in this subject, but I was trying to induce others to descend from the clouds. I agree with Dr. Cannon in regard to thyroxin. I did not doubt Dr. Cannon's facts—he reports what he finds under the conditions of his experiments. No matter how stupid or uncritical we physiologists sometimes are, we are at least honest, and there would be less folly and no fakes in the field of endocrinology if there was simple honesty all around, coupled with a more general recognition of the "post hoc" policy. Most people seem to have accepted Kendall's thyroxin as being the true thyroid hormone. In my judgment, the case is not proved. Several of the speakers considered untenable the prevalent view that endocrine physiology and glandular extract action are identical with sympathetic nerve action. That is one of the generalizations that have led us astray. I am sorry that neither Dr. Hoskins nor Dr. Rowntree discussed what to me seems the real crux in the practical application of endocrine material in the treatment of disease; that is, when are organ extracts indicated? The question whether one should use the pluriglandular "dope" obtained in commerce, do one's own mixing, or employ single substances is of minor importance. But when the most extensive and carefully controlled organotherapy, experimental and clinical, is without effect, should we not stop this therapy, at least until we know more about the content of the organ extracts, and the etiology of the maladies we are trying to cure by them? Is it not time to say: "Physician, heal thyself"—of endocrinitis?

Dr. L. F. Barker, Baltimore: The difficulty seems to be in distinguishing between facts and interpretations of facts. It has been hinted that physiologic facts are all right and that histopathologic facts are all right; and there has been a suggestion that clinical facts are not all right. But accurate clinical observations are just as truly facts as are physiologic or histologic observations. Clinicians see signs and symptoms that occur together, and we call these groups "syndromes." The "aeroplane flight" occurs when we try to interpret what these syndromes mean. Thus, we should sharply distinguish between "Graves' syndrome" and "hyperfunction of the thyroid." The one may really explain the other, or it may not. We ought, therefore, to have clearly in mind precisely what we mean when we make use of terms. When we say "Graves' syndrome" we mean a group of clinical signs and symptoms, and when we say that "hyperthyroidism" is responsible for "Graves' syndrome," we are propounding a physiologic theory of interpretation of the clinical syndrome. If medical men would keep these things

Digitized by Google

in mind, there would be less acrimonious discussion and fewer oblique hints of dishonest work!

Dr. R. G. Hoskins, Columbus, Ohio: The point I had intended to mention finally is the one Dr. Barker brought out: that there are many problems in this field that the physiologists cannot deal with. There are syndromes which involve endocrine glands that we cannot reproduce. The physiologist is responsible for the things he can do with the technic available to him. Also, there is responsibility on the clinicians to contribute from their point of view the phenomena which they see, and to put these contributions in a form and carry them out sufficiently, that they can ultimately be used in determining the important fundamental facts. While the problems are complex, it is not wise to be unduly impatient or pessimistic, but each one, clinician or laboratory investigator, with whatever technic is best suited to his problems, should press forward toward their solution.

Digitized by Google

INDEX

PAGE

Anesthesia, pulmonary aspiration of particulate matter, normally and during anesthesia; paper by H. J. Corper..... 64
Arteriosclerosis, production of, in rabbits, by diets rich in animal proteins; paper by L. H. Newburgh and S. Clarkson..... 113
Discussion 118
Ascariasis, recent additions to knowledge of; paper by B. H. Ransom 127
Aspiration, pulmonary, of particulate matter, normally and during anesthesia; paper by H. J. Corper..... 64
Aub, J. C.: paper on relation of internal secretions to metabolism... 171
Discussion on same..... 218
Baker, H. A.: discussion on endocrinology..... 216
Barker, L. F.: paper on endocrinology..... 148
Discussion on same..... 219
Bass, C. C.: discussion on standardization of laboratories..... 33
Black, J. H.: discussion on standardization of laboratories..... 36
Blumgarten, A. S.: discussion on endocrinology..... 216
Boothby, W. M.: discussion on endocrinology..... 214
Discussion on thyroid and diabetes..... 99
Brown, H. R.: discussion on cancer and gastric ulcer..... 48
Burdick, W.: discussion on standardization of laboratories..... 34
Burnett, F. L.: paper on intestinal rate and form of feces..... 38
Cannon, W. B.: paper on some conditions controlling internal secretion 158
Discussion on same..... 217
Carlson, A. J.: paper on hypofunction and hyperfunction of ductless glands..... 180
Discussion on same..... 218
Discussion on acute dilatation of stomach..... 62
Discussion on standardization of laboratories..... 35
Discussion on thyroid and diabetes..... 100
Clarkson, S.: paper on production of arteriosclerosis in rabbits by diets rich in animal proteins..... 113
Corper, H. J.: paper on pulmonary aspiration of particulate matter, normally and during anesthesia..... 64
Davis, D. J.: discussion on cancer and gastric ulcer..... 49
Diabetes, studies on relation of thyroid to pancreatic diabetes in dogs, with suggestions as to diabetes mellitus in man; paper by G. A. Friedman and J. Gottesman..... 79
Discussion 99
Dragstedt, C. A. : paper on acute dilatation of stomach..... 51
Dragstedt, L. R.: paper on acute dilatation of stomach..... 51
Discussion on same..... 63
Engelbach, W.: discussion on endocrinology..... 212
Feces, intestinal rate and form of; paper by F. L. Burnett..... 38
Friedman, G. A.: paper on relation of thyroid to pancreatic diabetes in dogs, with suggestions as to diabetes mellitus in man..... 79
Discussion on same..... 100
Gilbride, J. J.: discussion on acute dilatation of stomach..... 62
Discussion on cancer and gastric ulcer..... 48
Gottesman, J.: paper on relation of thyroid to pancreatic diabetes in dogs, with suggestions as to diabetes mellitus in man..... 79
Greene, C. W.: discussion on thyroid and diabetes..... 99

Digitized by Google

PAGE
Hillkowitz, P.: discussion on cancer and gastric ulcer..... 49
Discussion on standardization of laboratories..... 32
Horsley, J. S.: discussion on cancer and gastric ulcer..... 48
Hoskins, R. G.: paper on some principles of endocrinology applicable to organotherapy..... 204
Discussion on same..... 220
Huntoon, F. M.: paper on pneumococcus antibody solutions specific against types I, II and III..... 102
Discussion on same..... 112
Discussion on standardization of laboratories..... 34
Hyman, H. T.: discussion on endocrinology..... 214
Intestinal rate and form of feces; paper by F. L. Burnett..... 38
Kidney, congenital factor in chronic renal disease; paper by E. Weiss 120
Kolmer, J. A.: paper on state licensure applied to laboratorians.... 17
Discussion on cultivation of trichomonas..... 147
Discussion on pneumococcus antibody solutions..... 111
Laboratorians, state licensure applied to; paper by J. A. Kolmer... 17
Discussion 32
Laboratories, clinical, standardization of; paper by J. J. Moore..... 24
Discussion 32
Lackenbach, F. I.: discussion on standardization of laboratories.... 32
Luckhardt, A. B.: discussion on thyroid and diabetes..... 99
Lynch, K. M.: paper on cultivation of trichomonas and question of differentiation of flagellates..... 138
Discussion on same..... 147
Lyon, M. W., Jr.: discussion on experimental arteriosclerosis..... 118
MacCarty, W. C.: paper on does cancer arise in chronic gastric ulcer? 45
Discussion on same..... 50
Metabolism, relation of internal secretions to; paper by J. C. Aub. 171
Discussion 212
Moore, J. J.: paper on standardization of clinical laboratories..... 24
Discussion on same..... 36
Moorhead, J. J.: discussion on acute dilatation of stomach..... 61
Murphy, J. A.: discussion on pneumococcus antibody solutions..... 111
Newburgh, L. H.: paper on production of arteriosclerosis in rabbits by diets rich in animal proteins..... 113
Discussion on same..... 119
Opie, E. L.: discussion on cancer and gastric ulcer..... 49
Organotherapy, some principles of endocrinology applicable to; paper by R. C. Hoskins..... 204
Discussion 212
Pneumococcus antibody solutions specific against types I, II and and III; paper by F. M. Huntoon..... 102
Discussion 111
Ransom, B. H.: paper on some recent additions to knowledge of ascariasis 127
Rowntree, L. G.: discussion on endocrinology..... 213
Secretions, internal; paper by L. F. Barker..... 148
Discussion 212
Secretions, internal, hypofunction and hyperfunction of ductless glands, paper by A. J. Carlson..... 180
Discussion 212
Secretions, internal, relation of, to metabolism; paper by J. C. Aub 171
Discussion 212
Secretions, internal, some conditions controlling; paper by W. B. Cannon 158
Discussion 212
Spitz, H.: discussion on standardization of laboratories..... 35
Stewart, W. H.: discussion on cancer and gastric ulcer..... 49

Digitized by Google

PAGE

Stomach, acute dilatation of; paper by L. R. Dragstedt and C. A. Dragstedt 51
Discussion 61
Stomach, does cancer arise in chronic gastric ulcer? paper by W. C. MacCarty 45
Discussion 48
Thyroid, studies on relation of thyroid to pancreatic diabetes in dogs, with suggestions as to diabetes mellitus in man; paper by G. A. Friedman and J. Gottesman 79
Discussion 99
Timme, W.: discussion on endocrinology 215
Trichomonas, cultivation of, and question of differentiation of flagellates; paper by K. M. Lynch 138
Discussion 147
Weiss, E.: paper on congenital factor in chronic renal disease 120
Wilson, L. B.: discussion on endocrinology 217

Digitized by Google

Digitized by Google

Digitized by Google

Digitized by Google

UNIVERSITY OF MICHIGAN
3 9015 07028 2747

Digitized by Google